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(54) Title: ALPHA 1a ADRENERGIC RECEPTOR ANTAGONISTS

(57) Abstract

This invention relates to certain novel compounds and derivates thereof, their synthesis, and their use as alpha 1a adrenergic receptor antagonists. One application of these compounds is in the treatment of benign prostatic hyperplasia. These compounds are selective in their ability to relax smooth muscle tissue enriched in the alpha 1a receptor subtype without at the same time inducing hypotension. One such tissue is found surrounding the urethral lining. Therefore, one utility of the instant compounds is to provide acute relief to males suffering from benign prostatic hyperplasia, by permitting less hindered urine flow. Another utility of the instant compounds is provided by combination with a human 5-alpha reductase inhibitory compound, such that both acute and chronic relief from the effects of benign prostatic hyperplasia are achieved.

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TITLE OF THE INVENTION
ALPHA 1a ADRENERGIC RECEPTOR ANTAGONISTS

This application claims the benefit of U.S. Provisional
5 Application No. 60/050,959, filed June 18, 1997.

FIELD OF THE INVENTION:

This invention relates to certain novel compounds and
derivatives thereof, their synthesis, and their use as alpha 1a
10 adrenoceptor antagonists. More particularly, the compounds of the
present invention are useful for treating benign prostatic hyperplasia
(BPH).

BACKGROUND OF THE INVENTION

15 Human adrenergic receptors are integral membrane
proteins which have been classified into two broad classes, the alpha
and the beta adrenergic receptors. Both types mediate the action of the
peripheral sympathetic nervous system upon binding of
catecholamines, norepinephrine and epinephrine.

20 Norepinephrine is produced by adrenergic nerve endings,
while epinephrine is produced by the adrenal medulla. The binding
affinity of adrenergic receptors for these compounds forms one basis of
the classification: alpha receptors bind norepinephrine more strongly
than epinephrine and much more strongly than the synthetic compound
25 isoproterenol. The binding affinity of these hormones is reversed for the
beta receptors. In many tissues, the functional responses, such as
smooth muscle contraction, induced by alpha receptor activation are
opposed to responses induced by beta receptor binding.

Subsequently, the functional distinction between alpha and
30 beta receptors was further highlighted and refined by the
pharmacological characterization of these receptors from various
animal and tissue sources. As a result, alpha and beta adrenergic
receptors were further subdivided into alpha 1, alpha 2, β_1 , and β_2
subtypes. Functional differences between alpha 1 and alpha 2 receptors

have been recognized, and compounds which exhibit selective binding between these two subtypes have been developed.

For a general background on the alpha adrenergic receptors, the reader's attention is directed to Robert R. Ruffolo, Jr., a-

5 Adrenoreceptors: Molecular Biology, Biochemistry and Pharmacology,
(Progress in Basic and Clinical Pharmacology series, Karger, 1991),
wherein the basis of alpha 1/alpha 2 subclassification, the molecular
biology, signal transduction (G-protein interaction and location of the
significant site for this and ligand binding activity away from the 3'-
10 terminus of alpha adrenergic receptors), agonist structure-activity
relationships, receptor functions, and therapeutic applications for
compounds exhibiting alpha-adrenergic receptor affinity was explored.

The cloning, sequencing and expression of alpha receptor subtypes from animal tissues has led to the subclassification of the

15 alpha 1 receptors into alpha 1d (formerly known as alpha 1a or 1a/1d),
alpha 1b and alpha 1a (formerly known as alpha 1c) subtypes. Each
alpha 1 receptor subtype exhibits its own pharmacologic and tissue
specificities. The designation "alpha 1a" is the appellation recently
approved by the IUPHAR Nomenclature Committee for the previously
20 designated "alpha 1c" cloned subtype as outlined in the 1995 Receptor
and Ion Channel Nomenclature Supplement (Watson and Girdlestone,
1995). The designation alpha 1a is used throughout this application to
refer to this subtype. At the same time, the receptor formerly designated
alpha 1a was renamed alpha 1d. The new nomenclature is used
25 throughout this application. Stable cell lines expressing these alpha 1
receptor subtypes are referred to herein; however, these cell lines were
deposited with the American Type Culture Collection (ATCC) under the
old nomenclature. For a review of the classification of alpha 1
adrenoceptor subtypes, see, Martin C. Michel, et al., *Naunyn-*
30 *Schmiedeberg's Arch. Pharmacol.* (1995) 352:1-10.

The differences in the alpha adrenergic receptor subtypes have relevance in pathophysiologic conditions. Benign prostatic hyperplasia, also known as benign prostatic hypertrophy or BPH, is an illness typically affecting men over fifty years of age, increasing in
35 severity with increasing age. The symptoms of the condition include,

but are not limited to, increased difficulty in urination and sexual dysfunction. These symptoms are induced by enlargement, or hyperplasia, of the prostate gland. As the prostate increases in size, it impinges on free-flow of fluids through the male urethra.

5 Concomitantly, the increased noradrenergic innervation of the enlarged prostate leads to an increased adrenergic tone of the bladder neck and urethra, further restricting the flow of urine through the urethra.

In benign prostatic hyperplasia, the male hormone 5alpha-dihydrotestosterone has been identified as the principal culprit. The continual production of 5a-dihydrotestosterone by the male testes induces incremental growth of the prostate gland throughout the life of the male. Beyond the age of about fifty years, in many men, this enlarged gland begins to obstruct the urethra with the pathologic symptoms noted above.

The elucidation of the mechanism summarized above has resulted in the recent development of effective agents to control, and in many cases reverse, the pernicious advance of BPH. In the forefront of these agents is Merck & Co., Inc.'s product PROSCAR® (finasteride).
20 The effect of this compound is to inhibit the enzyme testosterone 5-a reductase, which converts testosterone into 5a-dihydrotestosterone, resulting in a reduced rate of prostatic enlargement, and often reduction in prostatic mass.

The development of such agents as PROSCAR® bodes well for the long-term control of BPH. However, as may be appreciated from the lengthy development of the syndrome, its reversal also is not immediate. In the interim, those males suffering with BPH continue to suffer, and may in fact lose hope that the agents are working sufficiently rapidly.

30 In response to this problem, one solution is to identify pharmaceutically active compounds which complement slower-acting therapeutics by providing acute relief. Agents which induce relaxation of the lower urinary tract tissue, by binding to alpha 1 adrenergic receptors, thus reducing the increased adrenergic tone due to the
35 disease, would be good candidates for this activity. Thus, one such agent

is alfuzosin, which is reported in EP 0 204597 to induce urination in cases of prostatic hyperplasia. Likewise, in WO 92/0073, the selective ability of the R(+) enantiomer of terazosin to bind to adrenergic receptors of the alpha1 subtype was reported. In addition, in WO 92/161213,

- 5 combinations of 5a-reductase inhibitory compounds and alpha1-adrenergic receptor blockers (terazosin, doxazosin, prazosin, bunazosin, indoramin, alfuzosin) were disclosed. However, no information as to the alpha 1d, alpha 1b, or alpha 1a subtype specificity of these compounds was provided as this data and its relevancy to the treatment
- 10 of BPH was not known. Current therapy for BPH uses existing non-selective alpha 1 antagonists such as prazosin (Minipress, Pfizer), Terazosin (Hytrin, Abbott) or doxazosin mesylate (Cardura, Pfizer). These non-selective antagonists suffer from side effects related to antagonism of the alpha 1d and alpha 1b receptors in the peripheral vasculature, e.g., hypotension and syncope.
- 15

The recent cloning of the human alpha 1a adrenergic receptor (ATCC CRL 11140) and the use of a screening assay utilizing the cloned human alpha 1a receptor enables identification of compounds which specifically interact with the human alpha 1a adrenergic

- 20 receptor. [PCT International Application Publication Nos. WO94/08040, published 14 April 1994 and WO94/10989, published 26 May 1994] As disclosed in the instant patent disclosure, a cloned human alpha 1a adrenergic receptor and a method for identifying compounds which bind the human alpha 1a receptor has now made possible the identification of
- 25 selective human alpha 1a adrenergic receptor antagonists useful for treating BPH. The instant patent disclosure discloses novel compounds which selectively bind to the human alpha 1a receptor. These compounds are further tested for binding to other human alpha 1 receptor subtypes, as well as counterscreened against other types of
- 30 receptors (e.g., alpha 2), thus defining the specificity of the compounds of the present invention for the human alpha 1a adrenergic receptor.

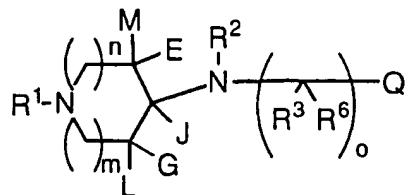
It is an object of the present invention to identify compounds which bind to the alpha 1a adrenergic receptor. It is a further object of the invention to identify compounds which act as antagonists of the alpha 1a adrenergic receptor. It is another object of the invention to

identify alpha 1a adrenergic receptor antagonist compounds which are useful agents for treating BPH in animals, preferably mammals, especially humans. Still another object of the invention is to identify alpha 1a adrenergic receptor antagonists which are useful for relaxing lower urinary tract tissue in animals, preferably mammals, especially humans.

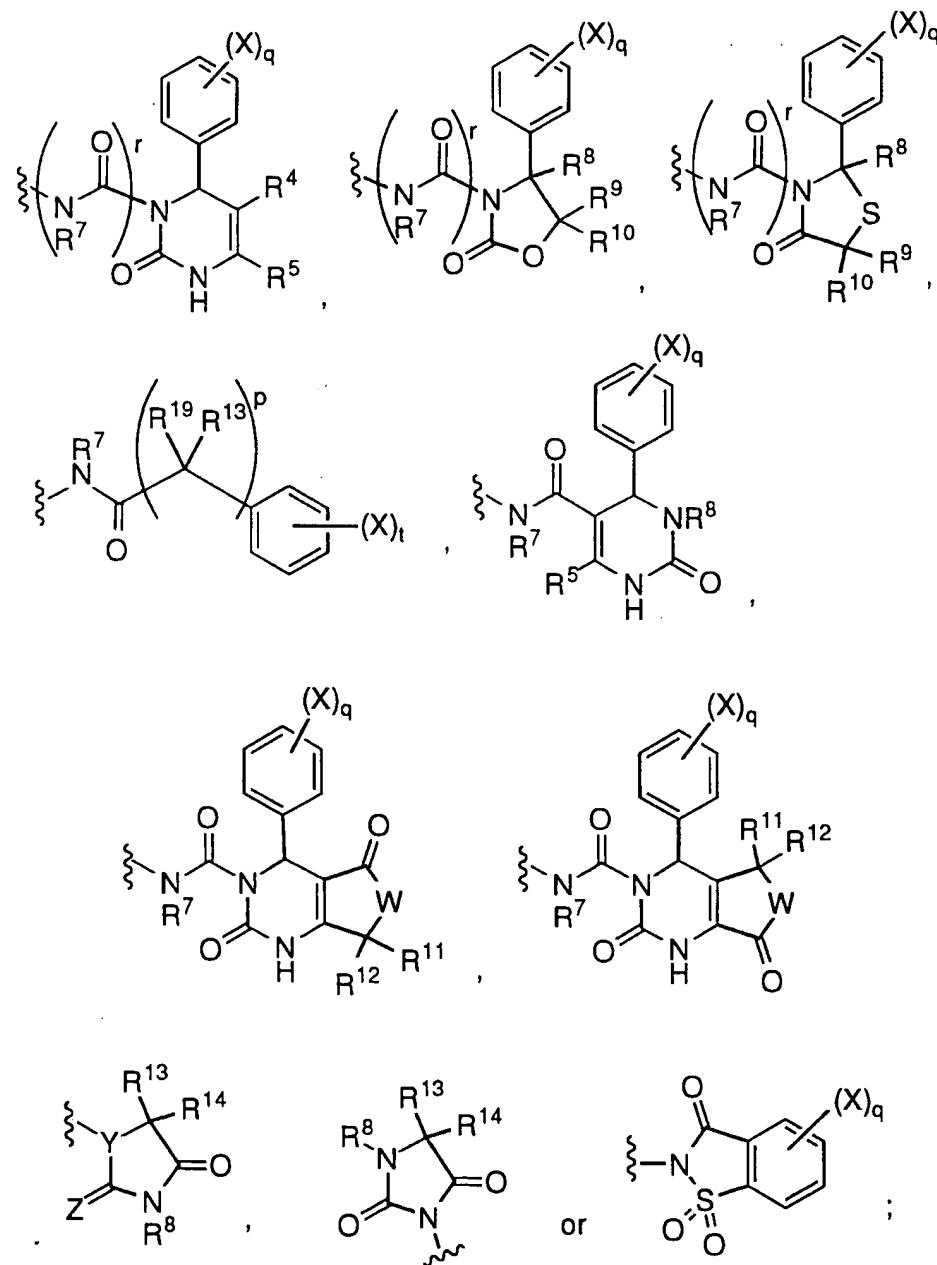
It has now been found that the compounds of the present invention are alpha 1a adrenergic receptor antagonists. Thus, the compounds of the present invention are useful for treating BPH in mammals. Additionally, it has been found that the alpha 1a adrenergic receptor antagonists of the present invention are also useful for relaxing lower urinary tract tissue in mammals.

SUMMARY OF THE INVENTION

The present invention provides compounds for the treatment of urinary obstruction caused by benign prostatic hyperplasia (BPH). The compounds antagonize the human alpha 1a adrenergic receptor at nanomolar and subnanomolar concentrations while exhibiting at least ten fold lower affinity for the alpha 1d and alpha 1b human adrenergic receptors and many other G-protein coupled receptors. This invention has the advantage over non-selective alpha 1 adrenoceptor antagonists of reduced side effects related to peripheral adrenergic blockade. Such side effects include hypotension, syncope, lethargy, etc. The compounds of the present invention have the structure:



wherein Q is selected from



5 E, G, L and M are each independently selected from hydrogen,
 C₁₋₈ alkyl, C₃₋₈ cycloalkyl, (CH₂)₀₋₄OR¹⁵, (CH₂)₀₋₄N(R¹⁶)₂,
 (CH₂)₀₋₄CN, (CH₂)₀₋₄CF₃, (CH₂)₀₋₄CO₂R¹⁶, (CH₂)₀₋₄CON(R¹⁶)₂,
 (CH₂)₀₋₄SO₂R¹⁶, or (CH₂)₀₋₄SO₂N(R¹⁶)₂;

J is selected from hydrogen, C₁-8 alkyl, C₃-8 cycloalkyl, (CH₂)₁₋₄OR¹⁵, (CH₂)₁₋₄N(R¹⁶)₂, (CH₂)₁₋₄CN, (CH₂)₀₋₄CF₃, (CH₂)₀₋₄CO₂R¹⁶, (CH₂)₀₋₄CON(R¹⁶)₂, (CH₂)₀₋₄SO₂R¹⁶, or (CH₂)₀₋₄SO₂N(R¹⁶)₂;

5

R¹ is selected from unsubstituted, mono- or poly-substituted phenyl wherein the substituents on the phenyl are independently selected from halogen, CF₃, cyano, nitro, N(R¹⁶)₂, NR¹⁶COR¹⁸, NR¹⁶COR²⁰, NR¹⁶CON(R¹⁸)₂, NR¹⁶CONR¹⁶CON(R¹⁸)₂, NR¹⁶SO₂R¹⁸,

10 NR¹⁶SO₂N(R¹⁸)₂, OR¹⁵, (CH₂)₀₋₄CO₂R¹⁶, (CH₂)₀₋₄CON(R¹⁶)₂, (CH₂)₀₋₄SO₂N(R¹⁶)₂, (CH₂)₀₋₄SO₂R¹⁵, (CH₂)₀₋₄SO₂R²² or

C₁₋₄ alkyl; or unsubstituted, mono- or poly-substituted pyridyl, pyrazinyl, pyrimidinyl, thienyl, thiazolyl, furanyl, isoquinolinyl,

15 quinazolinyl or naphthyl wherein the substituents on the pyridyl, pyrazinyl, pyrimidinyl, thienyl, thiazolyl, furanyl, isoquinolinyl, quinazolinyl or naphthyl are independently selected from CF₃, cyano, nitro, amino, NR¹⁶COR¹⁸, NR¹⁶COR²⁰, NR¹⁶SO₂R¹⁸, NR¹⁶CONR¹⁶CON(R¹⁸)₂, (CH₂)₀₋₄CO₂R¹⁶, (CH₂)₀₋₄CON(R¹⁶)₂,

20 (CH₂)₀₋₄SO₂N(R¹⁶)₂, (CH₂)₀₋₄SO₂R¹⁵, (CH₂)₀₋₄SO₂R²², phenyl, OR¹⁵, halogen,

C₁₋₄ alkyl or C₃-8 cycloalkyl;

R² and R⁷ are each independently selected from hydrogen, C₁-8 alkyl,

25 C₄-8 cycloalkyl, (CH₂)₀₋₄CO₂R¹⁶, (CH₂)₀₋₄CON(R¹⁶)₂, (CH₂)₀₋₄COR¹⁶, (CH₂)₂₋₄OR¹⁵, (CH₂)₁₋₄CF₃, (CH₂)₀₋₄SO₂R¹⁶, (CH₂)₀₋₄SO₂N(R¹⁶)₂ or (CH₂)₁₋₄CN;

R³, R⁶, R⁹ and R¹⁰ are each independently selected from hydrogen, C₁-8

30 alkyl, C₃-8 cycloalkyl, (CH₂)₂₋₄OR¹⁵ or (CH₂)₀₋₄CF₃;

R⁴ is selected from hydrogen, (CH₂)₀₋₄COR¹⁵, (CH₂)₀₋₄CN, (CH₂)₀₋₄CF₃,

(CH₂)₀₋₄CO₂R¹⁶, (CH₂)₀₋₄CON(R¹⁶)₂, (CH₂)₀₋₄SO₂R¹⁵ or

$(CH_2)_{0-4}SO_2N(R^{16})_2$;

R⁵ is selected from hydrogen, C₁₋₈ alkyl, C₃₋₈ cycloalkyl, (CH₂)₁₋₄OR¹⁵ or (CH₂)₀₋₄CF₃;

5

R⁸ is selected from hydrogen, C₁₋₈ alkyl, C₃₋₈ cycloalkyl, (CH₂)₂₋₄OR¹⁵ or (CH₂)₀₋₄CF₃;

10 R¹¹ and R¹² are each independently selected from hydrogen, C₁₋₈ alkyl or C₃₋₈ cycloalkyl;

15 R¹³ and R¹⁴ are each independently selected from hydrogen, C₁₋₈ alkyl, C₃₋₈ cycloalkyl, (CH₂)₁₋₄OR¹⁵, (CH₂)₀₋₄CF₃, unsubstituted, mono- or poly-substituted phenyl wherein the substituents on the phenyl are independently selected from halogen, CF₃, cyano, nitro, CO₂R¹⁶, OR¹⁵, (CH₂)₀₋₄CON(R¹⁶)₂, (CH₂)₀₋₄CO₂R¹⁶ or C₁₋₄ alkyl; or unsubstituted, mono- or poly-substituted: pyridyl, pyrazinyl, thienyl, furanyl or naphthyl wherein the substituents on the pyridyl, pyrazinyl, thienyl, furanyl or naphthyl are independently selected from CF₃, phenyl, OR¹⁵, halogen, C₁₋₄ alkyl or C₃₋₈ cycloalkyl;

20 R¹⁵ is selected from hydrogen, C₁₋₈ alkyl, C₃₋₈ cycloalkyl or (CH₂)₀₋₄CF₃;

25

R¹⁶ and R¹⁸ are each independently selected from hydrogen, C₁₋₈ alkyl, C₄₋₈ cycloalkyl or (CH₂)₁₋₄CF₃;

30 R¹⁹ is selected from hydrogen, C₁₋₈ alkyl, C₃₋₈ cycloalkyl, (CH₂)₀₋₄OR¹⁵ or (CH₂)₀₋₄CF₃;

R²⁰ is furanyl or C₁₋₈ alkyl furanyl;

R²² is piperazinyl or C₁₋₈ alkylpiperazinyl;

W is O or NR¹¹;

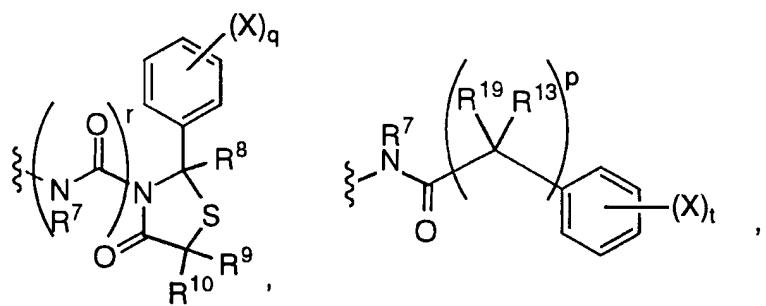
each X is independently selected from halogen, cyano, nitro, C₁₋₈ alkyl,
 5 C₃₋₈ cycloalkyl, (CH₂)₀₋₄OR¹⁵ or (CH₂)₀₋₄CF₃;

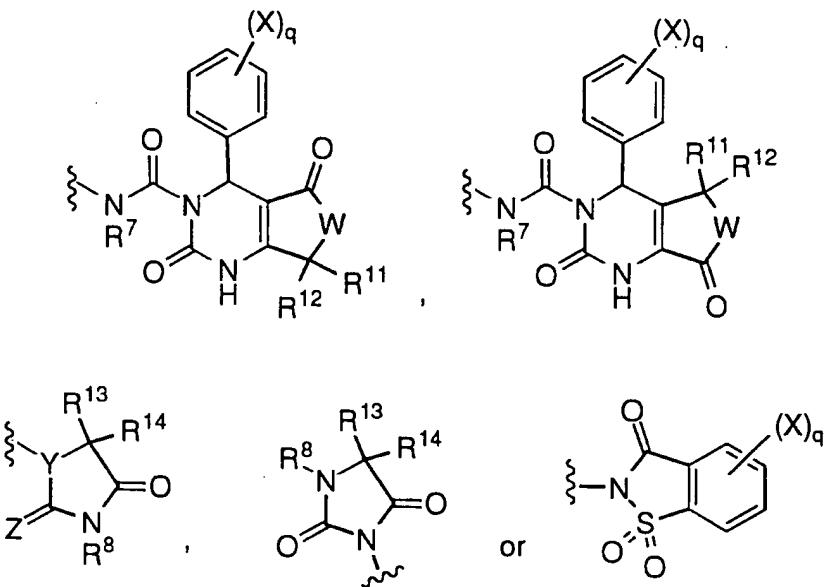
Y is CR¹⁵ or N;

Z is hydrogen, oxygen or sulphur;

10 m, n, p and q are each independently an integer from zero to four;
 o is an integer from two to five;
 r is an integer from zero to one;
 t is an integer from zero to five;
 15 and the pharmaceutically acceptable salts thereof.

In one aspect of the invention is the compound as just described with the proviso that: when R¹ is unsubstituted or mono-substituted phenyl; and R² is selected from hydrogen, C₁₋₈ alkyl, or (CH₂)₀₋₄COR¹⁶; and R⁷ is hydrogen; and M, E, J, G, L, R³ and R⁶ are
 20 each hydrogen; and n and m are each one; then Q is selected from





In a first embodiment of the invention are the compounds having the structure set forth above, wherein

5

R^1 is selected from unsubstituted, mono- or poly-substituted phenyl wherein the substituents on the phenyl are independently selected from halogen, CF_3 , cyano, nitro, $N(R^{16})_2$, $NR^{16}COR^{18}$, $NR^{16}CON(R^{18})_2$, $NR^{16}SO_2R^{18}$, $NR^{16}SO_2N(R^{18})_2$, OR^{15} , $(CH_2)0-4CO_2R^{16}$,

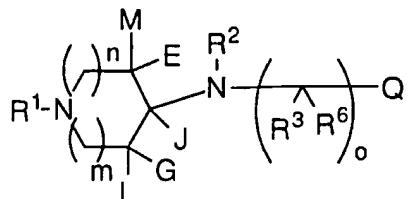
10 $(CH_2)0-4CON(R^{16})_2$, $(CH_2)0-4SO_2N(R^{16})_2$, $(CH_2)0-4SO_2R^{15}$, or C₁₋₄ alkyl; or unsubstituted, mono- or poly-substituted pyridyl, pyrazinyl, thienyl, thiazolyl, furanyl, quinazolinyl or naphthyl wherein the substituents on the pyridyl, pyrazinyl, thienyl, furanyl, quinazolinyl or naphthyl are independently selected from CF_3 , cyano, nitro, amino, $NR^{16}COR^{18}$, $NR^{16}SO_2R^{18}$, $(CH_2)0-4CO_2R^{16}$, $(CH_2)0-4CON(R^{16})_2$, $(CH_2)0-4SO_2N(R^{16})_2$, $(CH_2)0-4SO_2R^{15}$, phenyl, OR^{15} , halogen, C₁₋₄ alkyl or C₃₋₈ cycloalkyl; and

15

R^4 is selected from $(CH_2)0-4COR^{15}$, $(CH_2)0-4CN$, $(CH_2)0-4CF_3$, $(CH_2)0-4CO_2R^{16}$, $(CH_2)0-4CON(R^{16})_2$, $(CH_2)0-4SO_2R^{15}$ or $(CH_2)0-4SO_2N(R^{16})_2$; and all other variables are as previously defined; and the pharmaceutically acceptable salts thereof. An aspect of the

invention is the compound as just described in this embodiment with the proviso set forth in the preceding paragraph.

In a second embodiment of the invention is the compound of the formula



5

wherein

E, G, L, M and J are each independently selected from hydrogen, C₁₋₈ alkyl, C₃₋₈ cycloalkyl, or (CH₂)₀₋₄CF₃;

10

R¹ is selected from unsubstituted, mono-, di- or tri-substituted phenyl wherein the substituents on the phenyl are independently selected from halogen, CF₃, cyano, nitro, N(R¹⁶)₂, NR¹⁶COR¹⁸, NR¹⁶COR²⁰, NR¹⁶CON(R¹⁸)₂, NR¹⁶CONR¹⁶CON(R¹⁸)₂, NR¹⁶SO₂R¹⁸,

15 NR¹⁶SO₂N(R¹⁸)₂, OR¹⁵, (CH₂)₀₋₄CO₂R¹⁶,
 (CH₂)₀₋₄CON(R¹⁶)₂, (CH₂)₀₋₄SO₂N(R¹⁶)₂, (CH₂)₀₋₄SO₂R¹⁵,
 (CH₂)₀₋₄SO₂R²² or
 C₁₋₄ alkyl; or unsubstituted, mono-, di- or tri-substituted pyridyl,
 pyrazinyl, pyrimidinyl, thienyl, thiazolyl, furanyl, isoquinolinyl,
 20 quinazolinyl or naphthyl wherein the substituents on the pyridyl,
 pyrazinyl, pyrimidinyl, thienyl, thiazolyl, furanyl, isoquinolinyl,
 quinazolinyl or naphthyl are independently selected from CF₃, cyano,
 nitro, amino, NR¹⁶COR¹⁸, NR¹⁶COR²⁰, NR¹⁶SO₂R¹⁸,
 NR¹⁶CONR¹⁶CON(R¹⁸)₂, (CH₂)₀₋₄CO₂R¹⁶, (CH₂)₀₋₄CON(R¹⁶)₂,
 25 (CH₂)₀₋₄SO₂N(R¹⁶)₂, (CH₂)₀₋₄SO₂R¹⁵, (CH₂)₀₋₄SO₂R²², phenyl, OR¹⁵,
 halogen,
 C₁₋₄ alkyl or C₃₋₈ cycloalkyl;

30 R² and R⁷ are each independently selected from hydrogen, C₁₋₈ alkyl,
 C₄₋₈ cycloalkyl or (CH₂)₁₋₄CF₃;

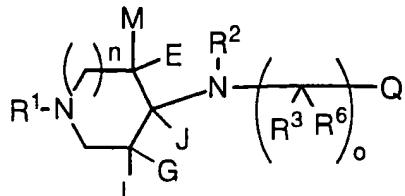
R¹³ and R¹⁴ are each independently selected from hydrogen, C₁₋₈ alkyl, C₃₋₈ cycloalkyl, (CH₂)₁₋₄OR¹⁵, (CH₂)₀₋₄CF₃, unsubstituted, mono-, di- or tri-substituted phenyl wherein the substituents on the phenyl are independently selected from halogen, CF₃, cyano, nitro, amino, OR¹⁵, (CH₂)₀₋₄CON(R¹⁶)₂, (CH₂)₀₋₄CO₂R¹⁶ or C₁₋₄ alkyl; or unsubstituted, mono-, di- or tri-substituted: pyridyl, thienyl, furanyl or naphthyl wherein the substituents on the pyridyl, thienyl, furanyl or naphthyl are independently selected from CF₃, phenyl, OR¹⁵, halogen, C₁₋₄ alkyl or C₃₋₈ cycloalkyl;

n is an integer from zero to two;

m is an integer from zero to one; and

15 o is an integer from two to four;
and all other variables are as originally defined above;
and the pharmaceutically acceptable salts thereof.

In a third embodiment of the invention is the compound of the formula



20

wherein E, G, L, M and J are each independently selected from hydrogen, C₁₋₈ alkyl, C₃₋₈ cycloalkyl, or (CH₂)₀₋₄CF₃;

R¹ is selected from unsubstituted, mono-, di- or tri-substituted phenyl
25 wherein the substituents on the phenyl are independently selected from halogen, CF₃, cyano, nitro, N(R¹⁶)₂, NR¹⁶COR¹⁸, NR¹⁶CON(R¹⁸)₂, NR¹⁶SO₂R¹⁸, NR¹⁶SO₂N(R¹⁸)₂, OR¹⁵, (CH₂)₀₋₄CO₂R¹⁶, (CH₂)₀₋₄CON(R¹⁶)₂, (CH₂)₀₋₄SO₂N(R¹⁶)₂, (CH₂)₀₋₄SO₂R¹⁵ or C₁₋₄ alkyl; or unsubstituted, mono-, di- or tri-substituted pyridyl, pyrazinyl, thienyl, thiazolyl, furanyl, quinazolinyl or naphthyl wherein

the substituents on the pyridyl, pyrazinyl, thienyl, thiazolyl, furanyl, quinazolinyl or naphthyl are independently selected from CF_3 , cyano, nitro, amino, $\text{NR}^{16}\text{COR}^{18}$, $\text{NR}^{16}\text{SO}_2\text{R}^{18}$, $(\text{CH}_2)0\text{-}4\text{CO}_2\text{R}^{16}$,

$(\text{CH}_2)0\text{-}4\text{CON}(\text{R}^{16})_2$, $(\text{CH}_2)0\text{-}4\text{SO}_2\text{N}(\text{R}^{16})_2$, $(\text{CH}_2)0\text{-}4\text{SO}_2\text{R}^{15}$, phenyl,

5 OR^{15} , halogen, $\text{C}_1\text{-}4$ alkyl or $\text{C}_3\text{-}8$ cycloalkyl;

R^2 and R^7 are each independently selected from hydrogen, $\text{C}_1\text{-}8$ alkyl, $\text{C}_4\text{-}8$ cycloalkyl or $(\text{CH}_2)1\text{-}4\text{CF}_3$;

10 R^{13} and R^{14} are each independently selected from hydrogen, $\text{C}_1\text{-}8$ alkyl, $\text{C}_3\text{-}8$ cycloalkyl, $(\text{CH}_2)1\text{-}4\text{OR}^{15}$, $(\text{CH}_2)0\text{-}4\text{CF}_3$, unsubstituted, mono-, di- or tri-substituted phenyl wherein the substituents on the phenyl are independently selected from halogen, CF_3 , cyano, nitro, amino, OR^{15} , $(\text{CH}_2)0\text{-}4\text{CON}(\text{R}^{16})_2$,

15 $(\text{CH}_2)0\text{-}4\text{CO}_2\text{R}^{16}$ or $\text{C}_1\text{-}4$ alkyl; or unsubstituted, mono-, di- or tri-substituted: pyridyl, thienyl, furanyl or naphthyl wherein the substituents on the pyridyl, thienyl, furanyl or naphthyl are independently selected from CF_3 , phenyl, OR^{15} , halogen, $\text{C}_1\text{-}4$ alkyl or $\text{C}_3\text{-}8$ cycloalkyl;

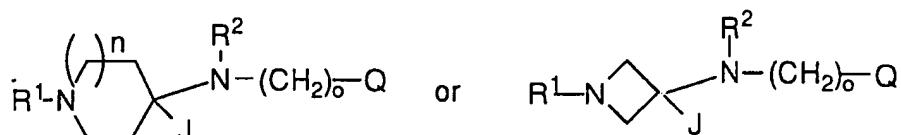
20

n is an integer from zero to two;

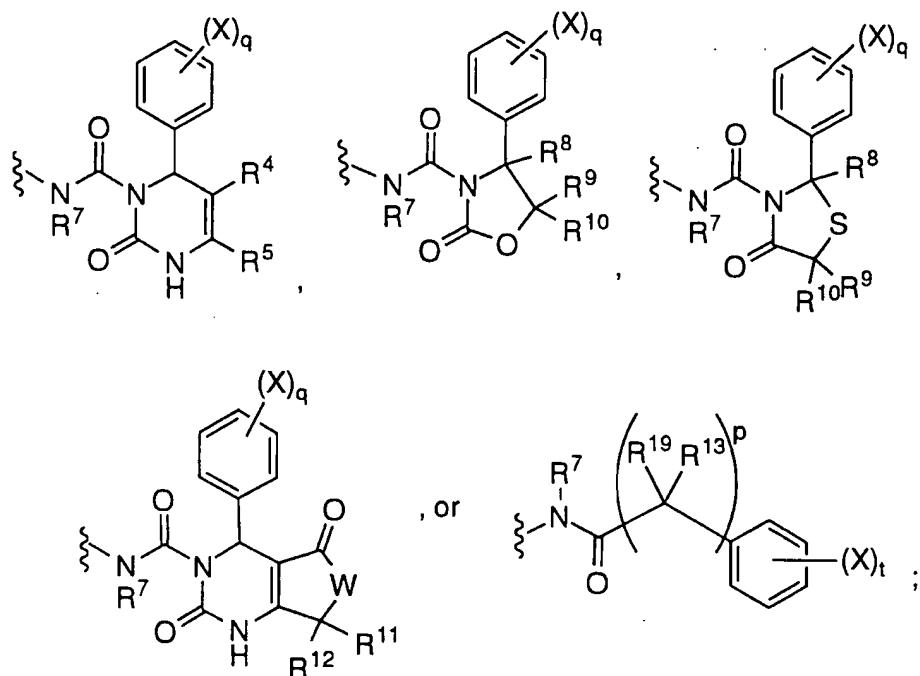
o is an integer from two to four;

and all other variables are as defined in the first embodiment; and the pharmaceutically acceptable salts thereof.

25 In a first class of the invention is the compound of the formula selected from



wherein Q is selected from



R^1 is selected from unsubstituted, mono-, di- or tri-substituted phenyl wherein the substituents on the phenyl are independently selected from halogen, CF_3 , cyano, nitro, $N(R^{16})_2$, $NR^{16}COR^{18}$, $NR^{16}COR^{20}$,

- 5 $NR^{16}CON(R^{18})_2$, $NR^{16}SO_2R^{18}$, OR^{15} , $(CH_2)_{0-2}CO_2R^{16}$, $(CH_2)_{0-2}CON(R^{16})_2$, $(CH_2)_{0-2}SO_2R^{15}$, $(CH_2)_{0-2}SO_2N(R^{16})_2$, $(CH_2)_{0-2}SO_2R^{22}$ or C_{1-4} alkyl; or unsubstituted, mono- or di-substituted pyridyl or pyrimidinyl wherein the substituents on the pyridyl or the pyrimidinyl are independently selected from CF_3 , cyano, nitro, amino, $NR^{16}COR^{18}$,
- 10 $NR^{16}COR^{20}$, $NR^{16}CON(R^{18})_2$, $NR^{16}SO_2R^{18}$, $(CH_2)_{0-2}CO_2R^{16}$, $(CH_2)_{0-2}CON(R^{16})_2$, $(CH_2)_{0-2}SO_2R^{15}$, $(CH_2)_{0-2}SO_2N(R^{16})_2$, OR^{15} , halogen, $(CH_2)_{0-2}SO_2R^{22}$ or C_{1-4} alkyl; or unsubstituted thiazolyl; or unsubstituted isoquinolinyl;
- 15 R^2 and R^7 are each independently selected from hydrogen, C_{1-6} alkyl, C_{4-6} cycloalkyl or $(CH_2)_{1-4}CF_3$;

R^4 is selected from hydrogen, COR^{15} , $(CH_2)_{0-2}CO_2R^{16}$, SO_2R^{15} or

$(CH_2)_{0-2}CON(R^{16})_2$;

R^5 is selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, $(CH_2)_{1-3}OR^{15}$ or $(CH_2)_{0-3}CF_3$; and

5

R^8 , R^9 and R^{10} are each independently selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, $(CH_2)_{2-4}OR^{15}$ or $(CH_2)_{0-2}CF_3$;

R^{13} is selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl,

10 $(CH_2)_{2-4}OR^{15}$, $(CH_2)_{0-2}CF_3$ or unsubstituted, mono- or di-substituted phenyl wherein the substituents on the phenyl are independently selected from halogen, CF₃, cyano, nitro, amino, OR¹⁵, CO₂R¹⁶ or C₁₋₄ alkyl;

15 R^{15} is selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl or $(CH_2)_{0-2}CF_3$;

R^{16} and R^{18} are each independently selected from hydrogen, C₁₋₆ alkyl, C₄₋₆ cycloalkyl or $(CH_2)_{1-2}CF_3$;

20

R^{19} is selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, $(CH_2)_{0-4}OR^{15}$ or $(CH_2)_{0-2}CF_3$;

p is an integer from one to two;

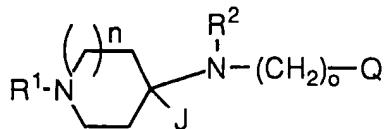
25 q is an integer from zero to three;

t is an integer from zero to four;

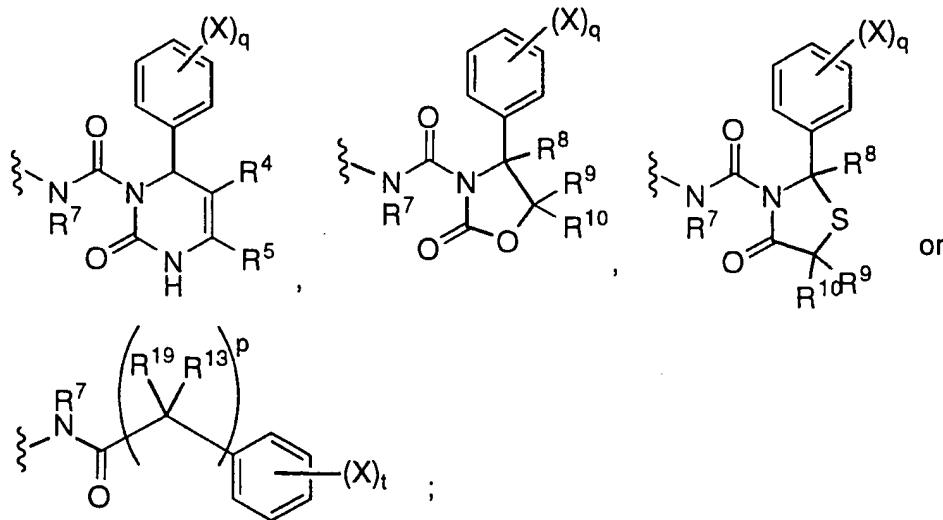
and all other variables are as defined previously in the second embodiment;

and the pharmaceutically acceptable salts thereof.

30 In a second class of the invention is the compound of the formula



wherein Q is selected from



R^1 is selected from unsubstituted, mono-, di- or tri-substituted phenyl

5 wherein the substituents on the phenyl are independently selected from halogen, CF₃, cyano, nitro, N(R¹⁶)₂, NR¹⁶COR¹⁸, NR¹⁶SO₂R¹⁸, OR¹⁵, (CH₂)₀₋₂CO₂R¹⁶, (CH₂)₀₋₂CON(R¹⁶)₂, (CH₂)₀₋₂SO₂R¹⁵, (CH₂)₀₋₂SO₂N(R¹⁶)₂ or C₁₋₄ alkyl; or unsubstituted, mono- or di-substituted pyridyl wherein the substituents on the pyridyl are independently selected from CF₃, cyano, nitro, amino, NR¹⁶COR¹⁸, NR¹⁶SO₂R¹⁸, (CH₂)₀₋₂CO₂R¹⁶, (CH₂)₀₋₂CON(R¹⁶)₂, (CH₂)₀₋₂SO₂R¹⁵, (CH₂)₀₋₂SO₂N(R¹⁶)₂, OR¹⁵, halogen or C₁₋₄ alkyl;

10 R² and R⁷ are each independently selected from hydrogen, C₁₋₆ alkyl, C₄₋₆ cycloalkyl or (CH₂)₁₋₄CF₃;

15

R^4 is selected from COR15, $(CH_2)_{0-2}CO_2R^{16}$, SO_2R^{15} or $(CH_2)_{0-2}CON(R^{16})_2$;

R^5 is selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, (CH₂)₁₋₃OR¹⁵ or (CH₂)₀₋₃CF₃; and

5 R^8 , R^9 and R^{10} are each independently selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, (CH₂)₂₋₄OR¹⁵ or (CH₂)₀₋₂CF₃;

R^{13} is selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, (CH₂)₂₋₄OR¹⁵, (CH₂)₀₋₂CF₃ or unsubstituted, mono- or di-substituted

10 phenyl wherein the substituents on the phenyl are independently selected from halogen, CF₃, cyano, nitro, amino, OR¹⁵, CO₂R¹⁶ or C₁₋₄ alkyl;

R^{15} is selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl or

15 (CH₂)₀₋₂CF₃;

R^{16} and R^{18} are each independently selected from hydrogen, C₁₋₆ alkyl, C₄₋₆ cycloalkyl or (CH₂)₁₋₂CF₃;

20 R^{19} is selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, (CH₂)₀₋₄OR¹⁵ or (CH₂)₀₋₂CF₃;

p is an integer from one to two;

q is an integer from zero to three;

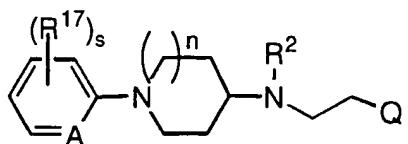
25 t is an integer from zero to four;

and all other variables are as defined previously in the third embodiment;

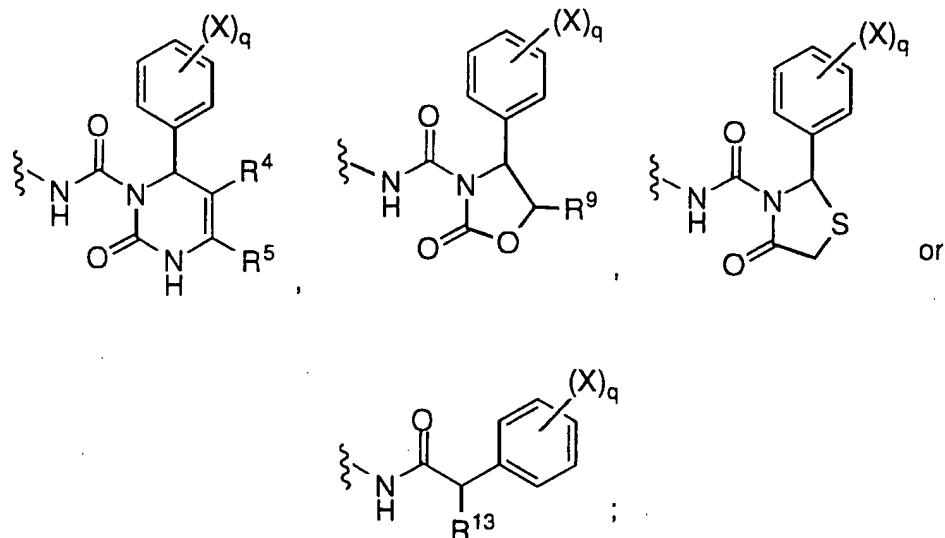
and the pharmaceutically acceptable salts thereof.

In a first subclass of the invention is the compound of the

30 formula



wherein Q is selected from



5 A is C-R¹⁷ or N;

R² is selected from hydrogen or CH₂CF₃;

R⁹ is selected from hydrogen or C₁₋₄ alkyl;

10

each R¹⁷ is independently selected from hydrogen, halogen, CF₃, cyano, nitro, amino, NR¹⁶COR¹⁸, NR¹⁶CON(R¹⁸)₂, NR¹⁶CONR¹⁶CON(R¹⁸)₂, NR¹⁶SO₂R¹⁸, NR¹⁶COR²⁰, OR¹⁵, CO₂R¹⁶, CON(R¹⁶)₂, SO₂N(R¹⁶)₂, SO₂R¹⁵ or C₁₋₄ alkyl;

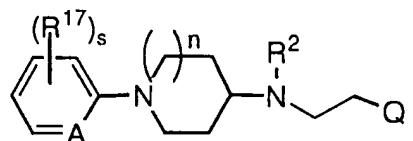
15

each X is halogen;

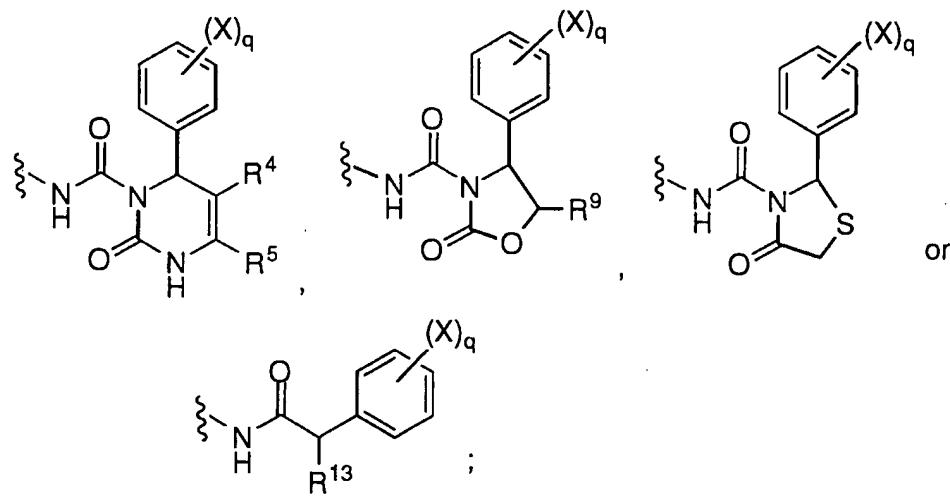
n is an integer from zero to one; and

q and s are each independently an integer from zero to two; and all other 20 variables are as defined above in the first class; and the pharmaceutically acceptable salts thereof.

In a second subclass of the invention is the compound of the formula



wherein Q is selected from



A is C-R¹⁷ or N;

5

R² is selected from hydrogen or CH₂CF₃;

R⁹ is selected from hydrogen or C₁₋₄ alkyl;

10 each R¹⁷ is independently selected from hydrogen, halogen, CF₃, cyano, nitro, amino, NR¹⁶COR¹⁸, NR¹⁶SO₂R¹⁸, OR¹⁵, CO₂R¹⁶, CON(R¹⁶)₂, SO₂N(R¹⁶)₂, SO₂R¹⁵ or C₁₋₄ alkyl;

each X is halogen;

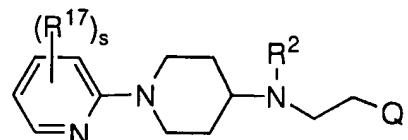
15

n is an integer from zero to one; and

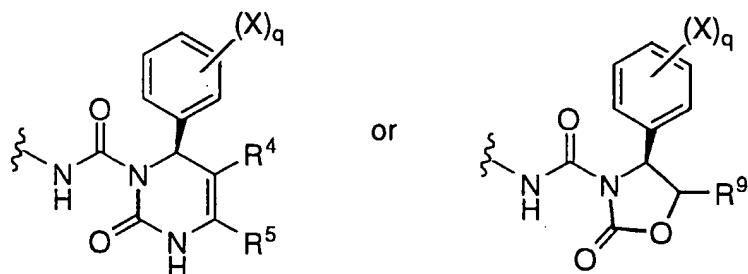
q and s are each independently an integer from zero to two;

and all other variables are as defined above in the second class; and the pharmaceutically acceptable salts thereof.

In a first illustration of the invention is the compound of the formula

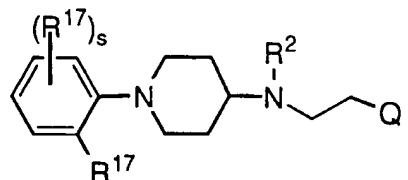


5 wherein Q is selected from

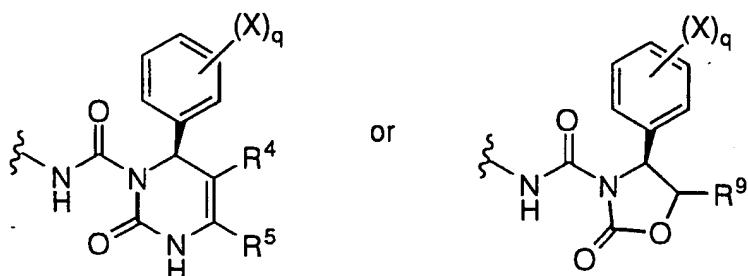


and all other variables are as defined above in the first subclass; and the pharmaceutically acceptable salts thereof.

10 In a second illustration of the invention is the compound of the formula



wherein Q is selected from

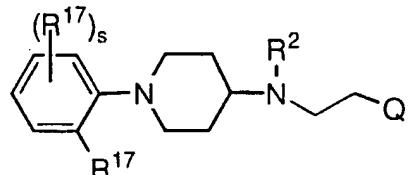


each R^{17} is independently selected from hydrogen, halogen, CF_3 , cyano, nitro, amino, $NHCONH_2$, $NHCONHCONH_2$, $NHCO$ -furanyl, $NHCONH$ $C1\text{-}4$ alkyl, $C1\text{-}4$ alkoxy, OCF_3 , OCH_2CF_3 , $CO_2\text{-}C1\text{-}4$ alkyl, $CONH_2$, SO_2NH_2 , $SO_2C1\text{-}4$ alkyl, $NHSO_2C1\text{-}4$ alkyl, $SO_2C1\text{-}4$

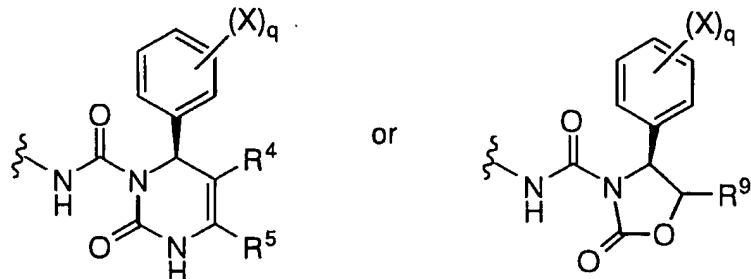
5 alkylpiperazinyl or $C1\text{-}4$ alkyl; and all other variables are as defined above in the first subclass; and the pharmaceutically acceptable salts thereof.

In a third illustration of the invention is the compound, of the formula

10



wherein Q is selected from



each R^{17} is independently selected from hydrogen, halogen, CF_3 , cyano, nitro, amino, $C1\text{-}4$ alkoxy, OCH_2CF_3 , $CO_2\text{-}C1\text{-}4$ alkyl, $CONH_2$ or $C1\text{-}4$

15 alkyl; and all other variables are as defined above in the second subclass; and the pharmaceutically acceptable salts thereof.

Exemplifying the invention is the compound selected from

20 N-(2-(1-(2-cyanophenyl)piperidin-4-ylamino)ethyl)-2-(3,4-difluorophenyl)acetamide;

4-(3,4-difluorophenyl)-6-methoxymethyl-3-(2-(1-(2-nitrophenyl)-piperidin-4-ylamino)ethylcarbamoyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

5 3-(2-(1-(2-cyanophenyl)piperidin-4-ylamino)ethylcarbamoyl)-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

10 4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(1-o-tolylpiperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

15 4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid (2-(1-(2-cyanophenyl)piperidin-4-ylamino)ethyl)amide;

15 4-(3,4-difluorophenyl)-6-methoxymethyl-3-(2-(1-(2-methoxyphenyl)piperidin-4-ylamino)ethylcarbamoyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

20 3-(2-(1-(2-cyano-4-trifluoromethylphenyl)piperidin-4-ylamino)ethylcarbamoyl)-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

25 3-(2-(1-(2-cyano-4-methylphenyl)piperidin-4-ylamino)ethylcarbamoyl)-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

30 3-(2-(1-(4-cyanophenyl)piperidin-4-ylamino)ethylcarbamoyl)-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

35 3-(2-(1-(2-cyano-4-fluorophenyl)-piperidin-4-ylamino)ethylcarbamoyl)-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

4-(3,4-difluorophenyl)-3-(2-(1-(2-methoxycarbonylphenyl)piperidin-4-ylamino)ethylcarbamoyl)-6-methoxymethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

5 4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid (2-((1-(2-cyanophenyl) piperidin-4-yl)-(2,2,2-trifluoroethyl)amino)ethyl)amide;

4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(1-(2,2,2-trifluoroethoxy)phenyl) piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-

10 10 tetrahydropyrimidine-5-carboxylic acid methyl ester;

4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid (2-(1-(2,2,2-trifluoroethoxy) phenyl)piperidin-4-ylamino)ethyl)amide;

15 15 4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid (2-(1-(2-cyanophenyl) pyrrolidin-3-ylamino)ethyl)amide;

2-3,4-difluorophenyl)-N-(2-(1-(2-nitrophenyl)piperidin-4-ylamino)ethyl)acetamide;

20

N-(2-(1-(2-aminophenyl)piperidin-4-ylamino)ethyl)-2-(3,4-difluorophenyl)acetamide;

2-(3,4-difluorophenyl)-4-oxothiazolidine-3-carboxylic acid (2-(1-(2-

25 cyanophenyl) piperidin-4-ylamino)ethyl)amide;

4-(3,4-difluorophenyl)-5-methyl-2-oxo-oxazolidine-3-carboxylic acid (2-(1-(2-cyanophenyl) piperidin-4-ylamino)ethyl)amide;

30 3-2-(1-(2-carbamoylphenyl)piperidin-4-ylamino)ethylcarbamoyl)-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid (2-(1-(2-

35 carbamoylphenyl) piperidin-4-ylamino)ethyl)amide;

4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid (2-(1-(4-fluoro-2-methoxycarbonylphenyl)piperidin-4-ylamino)ethyl)amide; or

5 4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid (2-(1-(2-methoxycarbonylphenyl)piperidin-4-ylamino)ethyl)amide;

and the pharmaceutically acceptable salts thereof.

Also exemplifying the invention is the compound selected
10 from

4S-4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid
(2-(2-(3-trifluoromethylpyridyl)piperidin-4-ylamino)ethyl)amide;

15 4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-(3-trifluoromethylpyridyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

20 4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-(3-methylpyridyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

25 4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-(5-methylpyridyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

30 4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-(5-trifluoromethylpyridyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

35 4S-4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid
(2-(2-(5-trifluoromethylpyridyl)piperidin-4-ylamino)ethylcarbamoyl)-

1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

4S-4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid
(2-(2-(4-trifluoromethylpyridyl)piperidin-4-ylamino)ethyl)amide;

5

4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-(6-methylpyridinyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

10 4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-(6-bromopyridyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-(3,6-

15 bistrifluoromethylpyridyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-(6-N-acetylaminopyridyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,

20 4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

and the pharmaceutically acceptable salts thereof.

Further exemplifying the invention is the compound selected from

25

4S-4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid
(2-(1-(2-methoxyphenyl)piperidin-4-ylamino)ethyl)amide;

4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(1-(2-

30 trifluoromethylphenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(1-(4-methoxyphenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,

35 4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

4S-4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid
(2-(1-(4-methoxyphenyl)piperidin-4-ylamino)ethyl)amide;

5 4S-4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid
(2-(2-(2,4-difluorophenyl)piperidin-4-ylamino)ethyl)amide;

4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(1-(2,4-
difluorophenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-
10 tetrahydropyrimidine-5-carboxylic acid methyl ester;

4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(1-(2-
sulfonamidophenyl)piperidin-4-ylamino)ethylcarbamoyl)-
1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

15 4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(1-(2-
methanesulfonylphenyl)piperidin-4-ylamino)ethylcarbamoyl)-
1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

20 4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(1-(2-
trifluormethylphenyl)piperidin-4-ylamino)ethylcarbamoyl)-
1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

25 4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(1-(2-
cyanophenyl)pyrrolodin-3-ylamino)ethylcarbamoyl)-1,2,3,4-
tetrahydropyrimidine-5-carboxylic acid methyl ester;

30 4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(1-(
phenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-
tetrahydropyrimidine-5-carboxylic acid methyl ester;

35 4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(1-(3-
fluorophenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-
tetrahydropyrimidine-5-carboxylic acid methyl ester;

4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(1-(4-carboxymethylphenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

5 4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(1-(2-cyano-5-fluorophenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

10 4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(1-(3,5-difluorophenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

15 4S-4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid (2-(1-(3,5-difluorophenyl)piperidin-4-ylamino)ethyl)amide;

20 4S-4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid (2-(1-(2-carboxymethylphenyl)piperidin-4-ylamino)ethyl)amide;

25 4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-(3,6-bistrifluoromethylpyridyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

30 4S-4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid (2-(1-(2-cyano-4-fluorophenyl)piperidin-4-ylamino)ethyl)amide;

25 4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-(3,5-dichlorophenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

30 4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-(2-N-sulfonylmethylaminophenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-aminophenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

5 4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-nitrophenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

10 4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-N-carboxamidoaminophenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

15 4S-4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-N-1-imidocarbonic diamidyl) phenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester

4S-4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid (2-(1-(2-nitrophenyl)piperidin-4-ylamino)ethyl)amide;

20 4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-N-(2-furanyl)carbonylaminophenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

25 4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-(4-N-methylpiperazinyl)sulfonylphenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

30 4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-(2-carboxymethylphenyl)piperidin-4-yl-1-methylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

(4S)-4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-(1-N-(3-N-methylureyl)phenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

and the pharmaceutically acceptable salts thereof.

An illustration of the invention is a pharmaceutical composition comprising a therapeutically effective amount of any of the compounds described above and a pharmaceutically acceptable carrier.

- 5 An example of the invention is a pharmaceutical composition made by combining any of the compounds described above and a pharmaceutically acceptable carrier. Another illustration of the invention is a process for making a pharmaceutical composition comprising combining any of the compounds described above and a
- 10 pharmaceutically acceptable carrier.

Another example of the invention is the composition further comprising a therapeutically effective amount of a testosterone 5-alpha reductase inhibitor. Preferably, the testosterone 5-alpha reductase inhibitor is a type 1, a type 2, both a type 1 and a type 2 (i.e., a three component combination comprising any of the compounds described above combined with both a type 1 testosterone 5-alpha reductase inhibitor and a type 2 testosterone 5-alpha reductase inhibitor) or a dual type 1 and type 2 testosterone 5-alpha reductase inhibitor. More preferably, the testosterone 5-alpha reductase inhibitor is a type 2 testosterone 5-alpha reductase inhibitor. Most preferably, the testosterone 5-alpha reductase inhibitor is finasteride.

- 15
- 20
- 25

More specifically illustrating the invention is a method of treating benign prostatic hyperplasia in a subject in need thereof which comprises administering to the subject a therapeutically effective amount of any of the compounds (or any of the compositions) described above.

Further exemplifying the invention is the method of treating BPH wherein the compound (or composition) additionally does not cause a fall in blood pressure at dosages effective to alleviate BPH.

- 30

Another illustration of the invention is the method of treating benign prostatic hyperplasia wherein the compound is administered in combination with a testosterone 5-alpha reductase inhibitor. Preferably, the testosterone 5-alpha reductase inhibitor is finasteride.

Further illustrating the invention is a method of inhibiting contraction of prostate tissue or relaxing lower urinary tract tissue in a subject in need thereof which comprises administering to the subject a therapeutically effective amount of any of the compounds (or any of the compositions) described above.

5 More specifically exemplifying the invention is the method of inhibiting contraction of prostate tissue or relaxing lower urinary tract tissue wherein the compound (or composition) additionally does not cause a fall in blood pressures at dosages effective to inhibit contraction 10 of prostate tissue.

10 More particularly illustrating the invention is the method of inhibiting contraction of prostate tissue or relaxing lower urinary tract tissue wherein the compound (or composition) is administered in combination with a testosterone 5-alpha reductase inhibitor; preferably, 15 the testosterone 5-alpha reductase inhibitor is finasteride.

More particularly exemplifying the invention is a method of 20 treating a disease which is susceptible to treatment by antagonism of the alpha 1a receptor which comprises administering to a subject in need thereof an amount of any of the compounds described above effective to treat the disease. Diseases which are susceptible to treatment by antagonism of the alpha 1a receptor include, but are not limited to, BPH, high intraocular pressure, high cholesterol, impotency, sympathetically mediated pain, migraine (see, K.A. Vatz, Headache 1997;37: 107-108) and cardiac arrhythmia.

25 An additional illustration of the invention is the use of any of the compounds described above in the preparation of a medicament for: a) the treatment of benign prostatic hyperplasia; b) relaxing lower urinary tract tissue; or c) inhibiting contraction of prostate tissue; in a subject in need thereof.

30 An additional example of the invention is the use of any of the alpha 1a antagonist compounds described above and a 5-alpha reductase inhibitor for the manufacture of a medicament for: a) treating benign prostatic hyperplasia; b) relaxing lower urinary tract tissue; or c) inhibiting contraction of prostate tissue which comprises an effective

amount of the alpha 1a antagonist compound and an effective amount of 5-alpha reductase inhibitor, together or separately.

DETAILED DESCRIPTION OF THE INVENTION

5 Representative compounds of the present invention exhibit high selectivity for the human alpha 1a adrenergic receptor. One implication of this selectivity is that these compounds display selectivity for lowering intraurethral pressure without substantially affecting diastolic blood pressure.

10 Representative compounds of this invention display submicromolar affinity for the human alpha 1a adrenergic receptor subtype while displaying at least ten-fold lower affinity for the human alpha1d and alpha1b adrenergic receptor subtypes, and many other G-protein coupled human receptors. Particular representative compounds

15 of this invention exhibit nanomolar and subnanomolar affinity for the human alpha 1a adrenergic receptor subtype while displaying at least 30 fold lower affinity for the human alpha1d and alpha1b adrenergic receptor subtypes, and many other G-protein coupled human receptors (e.g., serotonin, dopamine, alpha 2 adrenergic, beta adrenergic or

20 muscarinic receptors).

These compounds are administered in dosages effective to antagonize the alpha 1a receptor where such treatment is needed, as in BPH. For use in medicine, the salts of the compounds of this invention refer to non-toxic "pharmaceutically acceptable salts." Other salts may, 25 however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a 30 solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may 35 include alkali metal salts, e.g. sodium or potassium salts; alkaline

earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts. Thus, representative pharmaceutically acceptable salts include the following:

Acetate, Benzenesulfonate, Benzoate, Bicarbonate,
5 Bisulfate, Bitartrate, Borate, Bromide, Calcium, Camsylate, Carbonate, Chloride, Clavulanate, Citrate, Dihydrochloride, Edetate, Edisylate, Estolate, Esylate, Fumarate, Gluceptate, Gluconate, Glutamate, Glycolylarsanilate, Hexylresorcinate, Hydrabamine, Hydrobromide, Hydrochloride, Hydroxynaphthoate, Iodide, Isothionate, Lactate,
10 Lactobionate, Laurate, Malate, Maleate, Mandelate, Mesylate, Methylbromide, Methylnitrate, Methylsulfate, Mucate, Napsylate, Nitrate, N-methylglucamine ammonium salt, Oleate, Pamoate (Embonate), Palmitate, Pantothenate, Phosphate/diphosphate, Polygalacturonate, Salicylate, Stearate, Sulfate, Subacetate, Succinate,
15 Tannate, Tartrate, Teoclate, Tosylate, Triethiodide and Valerate.

Compounds of this invention are used to reduce the acute symptoms of BPH. Thus, compounds of this invention may be used alone or in conjunction with a more long-term anti-BPH therapeutics, such as testosterone 5-a reductase inhibitors, including PROSCAR® (finasteride). Aside from their utility as anti-BPH agents, these compounds may be used to induce highly tissue-specific, localized alpha 1a adrenergic receptor blockade whenever this is desired. Effects of this blockade include reduction of intra-ocular pressure, control of cardiac arrhythmias, and possibly a host of alpha 1a receptor mediated central nervous system events.

The present invention includes within its scope prodrugs of the compounds of this invention. In general, such prodrugs will be functional derivatives of the compounds of this invention which are readily convertible *in vivo* into the required compound. Thus, in the 30 methods of treatment of the present invention, the term "administering" shall encompass the treatment of the various conditions described with the compound specifically disclosed or with a compound which may not be specifically disclosed, but which converts to the specified compound *in vivo* after administration to the patient. Conventional procedures for the 35 selection and preparation of suitable prodrug derivatives are described,

for example, in "Design of Prodrugs," ed. H. Bundgaard, Elsevier, 1985. Metabolites of these compounds include active species produced upon introduction of compounds of this invention into the biological milieu.

Where the compounds according to the invention have at least one chiral center, they may accordingly exist as enantiomers. Where the compounds according to the invention possess two or more chiral centers, they may additionally exist as diastereoisomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention. Furthermore, some of the crystalline forms for compounds of the present invention may exist as polymorphs and as such are intended to be included in the present invention. In addition, some of the compounds of the present invention may form solvates with water (i.e., hydrates) or common organic solvents. Such solvates are also encompassed within the scope of this invention.

The term "alkyl" shall mean straight or branched chain alkanes of one to ten total carbon atoms, or any number within this range (i.e., methyl, ethyl, 1-propyl, 2-propyl, n-butyl, s-butyl, t-butyl, etc.).

The term "alkenyl" shall mean straight or branched chain alkenes of two to ten total carbon atoms, or any number within this range.

The term "aryl" as used herein, except where otherwise specifically defined, refers to unsubstituted, mono- or poly-substituted aromatic groups such as phenyl or naphthyl.

The term "cycloalkyl" shall mean cyclic rings of alkanes of three to eight total carbon atoms (i.e., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl).

Whenever the term "alkyl" or "aryl" or either of their prefix roots appear in a name of a substituent (e.g., aralkoxyaryloxy) it shall be interpreted as including those limitations given above for "alkyl" and "aryl." Designated numbers of carbon atoms (e.g., C₁₋₁₀) shall refer independently to the number of carbon atoms in an alkyl or cyclic alkyl moiety or to the alkyl portion of a larger substituent in which alkyl appears as its prefix root.

The term "halogen" shall include iodine, bromine, chlorine and fluorine.

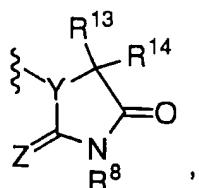
The term "substituted" shall be deemed to include multiple degrees of substitution by a named substituent. The term "poly-

5 substituted" as used herein shall include di-, tri-, tetra- and penta-
substitution by a named substituent. Preferably, a poly-substituted
moiety is di-, tri- or tetra-substituted by the named substituents, most
preferably, di- or tri-substituted.

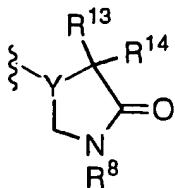
10 It is intended that the definition of any substituent or
variable (e.g., X, R¹⁶, R¹⁸) at a particular location in a molecule be
independent of its definitions elsewhere in that molecule. Thus, -
N(R¹⁶)₂ represents -NH₂, -NHCH₃, -NHC₂H₅, -N(CH₃)C₂H₅, etc. It is
understood that substituents and substitution patterns on the
compounds of the instant invention can be selected by one of ordinary
15 skill in the art to provide compounds that are chemically stable and that
can be readily synthesized by techniques known in the art as well as
those methods set forth below.

20 Where multiple substituent moieties are disclosed or
claimed, the substituted compound can be independently substituted by
one or more of the disclosed or claimed substituent moieties, singly or
plurally.

The term "Z is hydrogen," when referring to the "Q" group



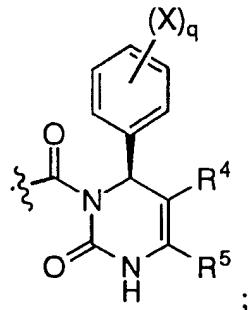
refers to the moiety



The term heterocycle or heterocyclic ring, as used herein, represents an unsubstituted or substituted stable 5- to 7-membered monocyclic ring system which may be saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms

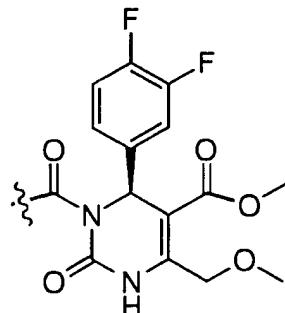
- 5 selected from N, O or S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic groups include, but is not
- 10 limited to, piperidinyl, piperazinyl, oxopiperazinyl, oxopiperidinyl, oxopyrrolidinyl, oxoazepinyl, azepinyl, pyrrolyl, pyrrolidinyl, furanyl, thieryl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isooxazolyl, isoxazolidinyl, morpholinyl, thiazolyl,
- 15 thiazolidinyl, isothiazolyl, thiadiazolyl, tetrahydropyranyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, and oxadiazolyl. Morpholino is the same as morpholinyl.

The terms "(+)-DHP" and "DHP" as used herein, refers to a dihydropyrimidinone group of the formula



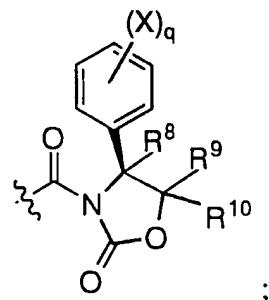
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for example:

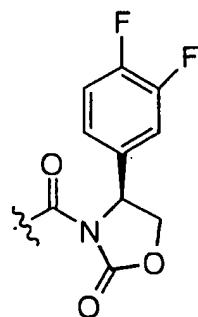


The term "activated (+)-DHP," as used herein, refers to a *N*-3-(activated)carbamate of the desired dihydropyrimidinone where the activating group is, for example, a p-nitrophenyloxy group. A specific 5 example of an activated (+)-DHP is 4-(3,4-difluorophenyl)-5-methoxycarbonyl-6-methoxymethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-3-carboxylic acid (4-nitrophenyl ester), also referred to as the compound 2.

The term "(S)-oxa" as used herein, refers to an 10 oxazolidinone group of the formula



for example,



The term "activated (S)-oxa" as used herein, refers to an N-(activated)carbamate of the desired oxazolidinone where the activating group is, for example, a p-nitrophenyloxy group. A specific example of an activated (S)-oxa group is 4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-5 carboxylic acid 4-nitrophenyl ester (i.e., compound 3).

The term "thienyl," as used herein, refers to the group



The term "selective alpha 1a adrenergic receptor antagonist," as used herein, refers to an alpha 1a antagonist compound 10 which is at least ten fold selective for the human alpha 1a adrenergic receptor as compared to the human alpha 1b, alpha 1d, alpha 2a, alpha 2b and alpha 2c adrenergic receptors.

The term "lower urinary tract tissue," as used herein, refers to and includes, but is not limited to, prostatic smooth muscle, the 15 prostatic capsule, the urethra and the bladder neck.

The term "subject," as used herein refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment.

The term "therapeutically effective amount" as used 20 herein means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disease being treated.

25 The present invention also provides pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or 30 suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation

or insufflation. Alternatively, the compositions may be presented in a form suitable for once-weekly or once-monthly administration; for example, an insoluble salt of the active compound, such as the decanoate salt, may be adapted to provide a depot preparation for

- 5 intramuscular injection. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g.
- 10 water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that
- 15 the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel
- 20 composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to
- 25 resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and
- 30 cellulose acetate.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as

5 cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or 10 gelatin.

Where the processes for the preparation of the compounds according to the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The compounds may be prepared in 15 racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The compounds may, for example, be resolved into their component enantiomers by standard techniques, such as the formation of diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-p-toluoyl-d-tartaric 20 acid and/or (+)-di-p-toluoyl-l-tartaric acid followed by fractional crystallization and regeneration of the free base. The compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary. Alternatively, the compounds may be resolved using a chiral 25 HPLC column.

During any of the processes for preparation of the compounds of the present invention, it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting 30 groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The specificity of binding of compounds showing affinity for the alpha 1a receptor is shown by comparing affinity to membranes obtained from transfected cell lines that express the alpha 1a receptor and membranes from cell lines or tissues known to express other types 5 of alpha (e.g., alpha 1d, alpha 1b) or beta adrenergic receptors. Expression of the cloned human alpha 1d, alpha 1b, and alpha 1a receptors and comparison of their binding properties with known selective antagonists provides a rational way for selection of compounds and discovery of new compounds with predictable pharmacological 10 activities. Antagonism by these compounds of the human alpha 1a adrenergic receptor subtype may be functionally demonstrated in anesthetized animals. These compounds may be used to increase urine flow without exhibiting hypotensive effects.

The ability of compounds of the present invention to 15 specifically bind to the alpha 1a receptor makes them useful for the treatment of BPH. The specificity of binding of compounds showing affinity for the alpha 1a receptor is compared against the binding affinities to other types of alpha or beta adrenergic receptors. The human alpha adrenergic receptor of the 1a subtype was recently 20 identified, cloned and expressed as described in PCT International Application Publication Nos. WO94/08040, published 14 April 1994 and WO 94/21660, published 29 September 1994. The cloned human alpha 1a receptor, when expressed in mammalian cell lines, is used to discover ligands that bind to the receptor and alter its function. Expression of the 25 cloned human alpha 1d, alpha 1b, and alpha 1a receptors and comparison of their binding properties with known selective antagonists provides a rational way for selection of compounds and discovery of new compounds with predictable pharmacological activities.

Compounds of this invention exhibiting human alpha 1a 30 adrenergic receptor antagonism may further be defined by counterscreening. This is accomplished according to methods known in the art using other receptors responsible for mediating diverse biological functions. [See e.g., PCT International Application Publication No. WO94/10989, published 26 May 1994; U.S. Patent No. 5,403,847, issued 35 April 4, 1995]. Compounds which are both selective amongst the various

human alpha1 adrenergic receptor subtypes and which have low affinity for other receptors, such as the alpha2 adrenergic receptors, the β -adrenergic receptors, the muscarinic receptors, the serotonin receptors, and others are particularly preferred. The absence of these non-specific

5 activities may be confirmed by using cloned and expressed receptors in an analogous fashion to the method disclosed herein for identifying compounds which have high affinity for the various human alpha1 adrenergic receptors. Furthermore, functional biological tests are used to confirm the effects of identified compounds as alpha 1a adrenergic
10 receptor antagonists.

The present invention also has the objective of providing suitable topical, oral, systemic and parenteral pharmaceutical formulations for use in the novel methods of treatment of the present invention. The compositions containing compounds of this invention

15 as the active ingredient for use in the specific antagonism of human alpha 1a adrenergic receptors can be administered in a wide variety of therapeutic dosage forms in conventional vehicles for systemic administration. For example, the compounds can be administered in such oral dosage forms as tablets, capsules (each including timed
20 release and sustained release formulations), pills, powders, granules, elixirs, tinctures, solutions, suspensions, syrups and emulsions, or by injection. Likewise, they may also be administered in intravenous (both bolus and infusion), intraperitoneal, subcutaneous, topical with or without occlusion, or intramuscular
25 form, all using forms well known to those of ordinary skill in the pharmaceutical arts. An effective but non-toxic amount of the compound desired can be employed as an alpha 1a antagonistic agent.

Advantageously, compounds of the present invention
30 may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of
35 transdermal skin patches well known to those of ordinary skill in

that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

The dosage regimen utilizing the compounds of the

- 5 present invention is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound thereof employed. A physician or veterinarian of ordinary skill can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition. Optimal precision in achieving concentration of drug within the range that yields efficacy without toxicity requires a regimen based on the kinetics of the drug's
- 10 availability to target sites. This involves a consideration of the distribution, equilibrium, and elimination of a drug.
- 15

In the methods of the present invention, the compounds herein described in detail can form the active ingredient, and are typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

- 20
- 25 For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and
- 30 coloring agents can also be incorporated into the mixture. Suitable binders include, without limitation, starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like.
- 35 Lubricants used in these dosage forms include, without limitation,

sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like.

Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

5 The liquid forms in suitably flavored suspending or dispersing agents such as the synthetic and natural gums, for example, tragacanth, acacia, methyl-cellulose and the like. Other dispersing agents which may be employed include glycerin and the like. For parenteral administration, sterile suspensions and solutions are
10 desired. Isotonic preparations which generally contain suitable preservatives are employed when intravenous administration is desired.

15 The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

20 Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinyl-pyrrolidone, pyran copolymer, polyhydroxypropylmethacryl-amidephenol, polyhydroxy-ethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues.
25 Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydro-pyrans, polycyanoacrylates and cross-linked or
30 amphipathic block copolymers of hydrogels.

Compounds of this invention may be administered in any of the foregoing compositions and according to dosage regimens established in the art whenever specific blockade of the human alpha 1a adrenergic receptor is required.

The daily dosage of the products may be varied over a wide range from 0.01 to 1,000 mg per adult human per day. For oral administration, the compositions are preferably provided in the form of tablets containing 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0 and 5 100 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. A medicament typically contains from about 0.01 mg to about 500 mg of the active ingredient, preferably, from about 1 mg to about 100 mg of active ingredient. An effective amount of the drug is ordinarily supplied at a dosage level of 10 from about 0.0002 mg/kg to about 20 mg/kg of body weight per day. Preferably, the range is from about 0.001 to 10 mg/kg of body weight per day, and especially from about 0.001 mg/kg to 7 mg/kg of body weight per day. The compounds may be administered on a regimen of 1 to 4 times per day.

15 Compounds of this patent disclosure may be used alone at appropriate dosages defined by routine testing in order to obtain optimal antagonism of the human alpha 1a adrenergic receptor while minimizing any potential toxicity. In addition, co-administration or sequential administration of other agents which alleviate the effects of 20 BPH is desirable. Thus, in one embodiment, this includes administration of compounds of this invention and a human testosterone 5-a reductase inhibitor. Included with this embodiment are inhibitors of 5-alpha reductase isoenzyme 2. Many such compounds are now well known in the art and include such compounds as 25 PROSCAR®, (also known as finasteride, a 4-Aza-steroid; see US Patents 4,377,584 and 4,760,071, for example). In addition to PROSCAR®, which is principally active in prostatic tissue due to its selectivity for human 5-a reductase isozyme 2, combinations of compounds which are specifically active in inhibiting testosterone 5-alpha reductase isozyme 1 30 and compounds which act as dual inhibitors of both isozymes 1 and 2, are useful in combination with compounds of this invention. Compounds that are active as 5a-reductase inhibitors have been described in WO93/23420, EP 0572166; WO 93/23050; WO93/23038, ; WO93/23048; WO93/23041; WO93/23040; WO93/23039; WO93/23376; 35 WO93/23419, EP 0572165; WO93/23051.

The dosages of the alpha 1a adrenergic receptor and testosterone 5-alpha reductase inhibitors are adjusted when combined to achieve desired effects. As those skilled in the art will appreciate, dosages of the 5-alpha reductase inhibitor and the alpha

- 5 1a adrenergic receptor antagonist may be independently optimized and combined to achieve a synergistic result wherein the pathology is reduced more than it would be if either agent were used alone. In accordance with the method of the present invention, the individual components of the combination can be administered separately at
- 10 different times during the course of therapy or concurrently in divided or single combination forms. The instant invention is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly.

- 15 Thus, in one preferred embodiment of the present invention, a method of treating BPH is provided which comprises administering to a subject in need of treatment any of the compounds of the present invention in combination with finasteride effective to treat BPH. The dosage of finasteride administered to the subject is
- 20 about 0.01 mg per subject per day to about 50 mg per subject per day in combination with an alpha 1a antagonist. Preferably, the dosage of finasteride in the combination is about 0.2 mg per subject per day to about 10 mg per subject per day, more preferably, about 1 to about 7 mg per subject per day, most preferably, about 5 mg per subject per day.
- 25

- 30 For the treatment of benign prostatic hyperplasia, compounds of this invention exhibiting alpha 1a adrenergic receptor blockade can be combined with a therapeutically effective amount of a 5a-reductase 2 inhibitor, such as finasteride, in addition to a 5a-reductase 1 inhibitor, such as 4,7b-dimethyl-4-aza-5a-cholestane-3-one, in a single oral, systemic, or parenteral pharmaceutical dosage formulation. Alternatively, a combined therapy can be employed wherein the alpha 1a adrenergic receptor antagonist and the 5a-reductase 1 or 2 inhibitor are administered in separate oral, systemic, or parenteral dosage formulations. See, e.g., U.S. Patent
- 35

No.'s 4,377,584 and 4,760,071 which describe dosages and formulations for 5a-reductase inhibitors.

Abbreviations used in the instant specification, particularly the Schemes and Examples, are as follows:

5

Aq = aqueous

Ac = acetyl

AcOH = acetic acid

BCE = bromochloroethane

10

BINAP = 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl

Boc or BOC = t-butyloxycarbonyl

BOPCl = bis(2-oxo-3-oxazolidinyl)phosphinic chloride

Cbz-Cl = benzyloxycarbonyl chloride

dba = dibenzylideneacetone

15

DEAD = diethylazodicarboxylate

DMF = N,N-dimethylformamide

DMSO = dimethylsulfoxide

EDCI = 1-(3-dimethylaminopropyl)-3-ethylcarbodimide hydrochloride

20

Et = ethyl

Et₃N = triethylamine

EtOAc = ethyl acetate

EtOH = ethanol

FABLRMS = fast atom bombardment low resolution mass spectroscopy

25

HPLC = high performance liquid chromatography

HOAc = acetic acid

HOEt = 1-hydroxy benzotriazole hydrate

i-PrOH = 2-propanol

30

i-Pr₂NEt = diisopropylethylamine

LAH = lithium aluminum hydride

mCPBA = meta-chloroperbenzoic acid

Me = methyl

MeOH = methanol

35

NMR = nuclear magnetic resonance

PCTLC = preparative centrifugal thin layer chromatography

PEI = polyethylenimine

Ph = phenyl

5 pTOS = p-toluenesulfonic acid

RT = retention time

TEBAC = benzyltriethylammonium chloride

TFA = trifluoroacetic acid

THF = tetrahydrofuran

10 TLC = thin layer chromatography

TMS = trimethylsilyl

The compounds of the present invention can be prepared readily according to the following reaction schemes and examples, or

15 modifications thereof, using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are themselves known to those of ordinary skill in this art, but are not mentioned in greater detail. Unless otherwise indicated, all variables are as defined above.

20 The preparation of key intermediates for the compounds of the present invention was accomplished via either Pd mediated coupling reactions or direct nucleophilic displacement, as outlined in Schemes 1 and 2. The products, typically ketals, were deketalized under acidic conditions. The resulting ketones can be further elaborated, for

25 instance, via enolate alkylation. The resultant alpha substituted ketones were further elaborated by reductive amination with mono or unprotected diamino portions. After deprotection of the required intermediates, the selective acylation of the primary amines was accomplished by treatment with nearly equimolar quantities of the 30 activated termini species (i.e., the "Q" groups).

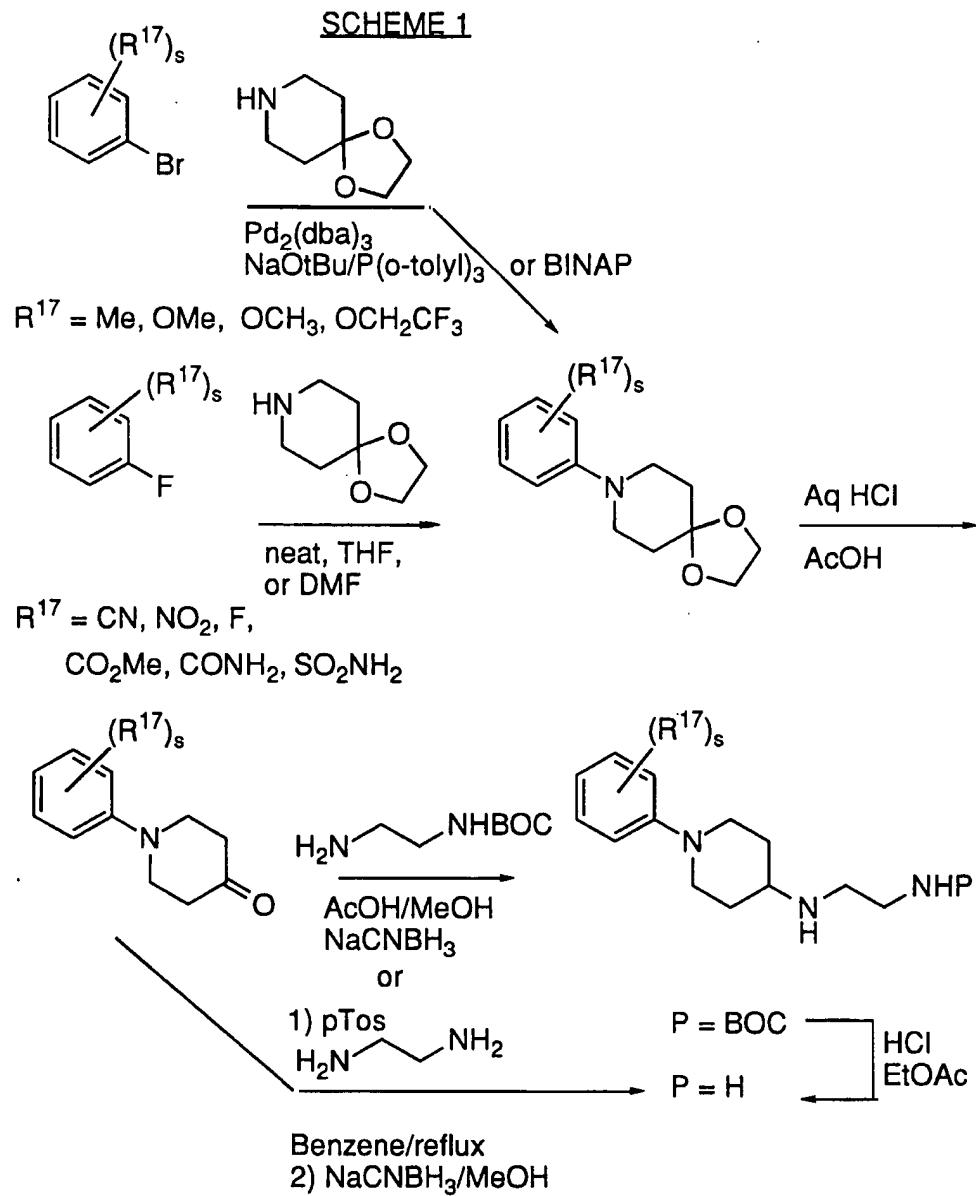
The activated termini species comprising the "Q" groups are readily prepared by one of ordinary skill in the art. For example, oxazolidinones are prepared and activated in general by published and well developed chemistry, in particular, of Evans. [Evans, D.A.; Nelson, 35 J.V.; Taber, T.R. *Top. Stereochem.* 13, 1 (1982)] The starting materials,

in general, are natural and unnatural amino acids. For instance, some of the preferred compounds are prepared from substituted phenyl glycine derivatives, which after reduction of the carboxylate and a phosgene equivalent mediated cyclization provides the substituted 5 oxazolidinone ring system. Deprotonation with n-butyl lithium and addition to a THF solution of p-nitrophenylchloroformate produces the stable, isolable "activated"oxazolidinone (oxa).

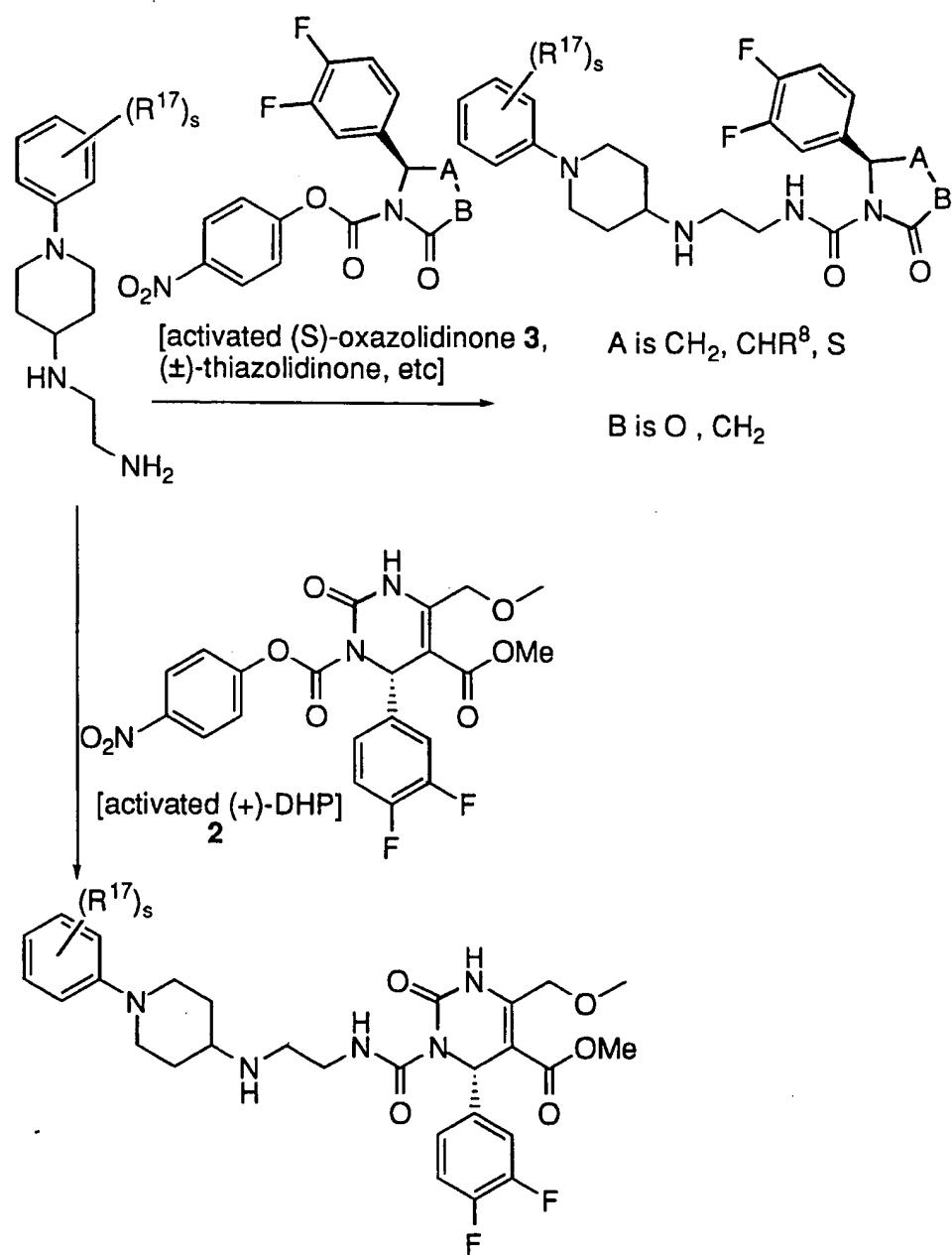
Dihydropyrimidinones are prepared by condensation reaction of the aldehyde, urea and a 1,3-acetoacetate type derivative 10 catalyzed by a Lewis Acid, a copper (I) species and acetic acid. Activation was accomplished by treatment with a strong base, for instance, LiN(TMS)2, followed by addition to a THF solution of p-nitrophenylchloroformate.

Hydantoins and cycloimide were prepared in two chemical 15 steps from ketones as outlined in the literature. More specifically, hydantoins were prepared according to known methodology, e.g., J.J. Edmunds et al., J. Med. Chem. 1995, 38, pp. 3759-3771; J.H. Poupaert et al., J. Chem. Res. 1979, pp. 174-175. Saccharins were prepared according to known methods, e.g., page 40 and Examples 21 and 22 of 20 PCT International Application Publication No. WO96/25934, published August 29, 1996.

The dihydropyrimidinones and oxazolidinones were synthesized independently in racemic form, and then separated utilizing preparative chiral HPLC. Their optical rotations were 25 recorded. Then they were activated and reacted with prerequisite amines. From the receptor binding studies, a preferred isomer was identified, the (+) rotational isomer in each case. The absolute configurations were determined to be (S) for both the dihydropyrimidinones and oxazolidinones by correlating their optical 30 rotations with x-ray crystal structures obtained of fragments involved in the production of the antagonists.

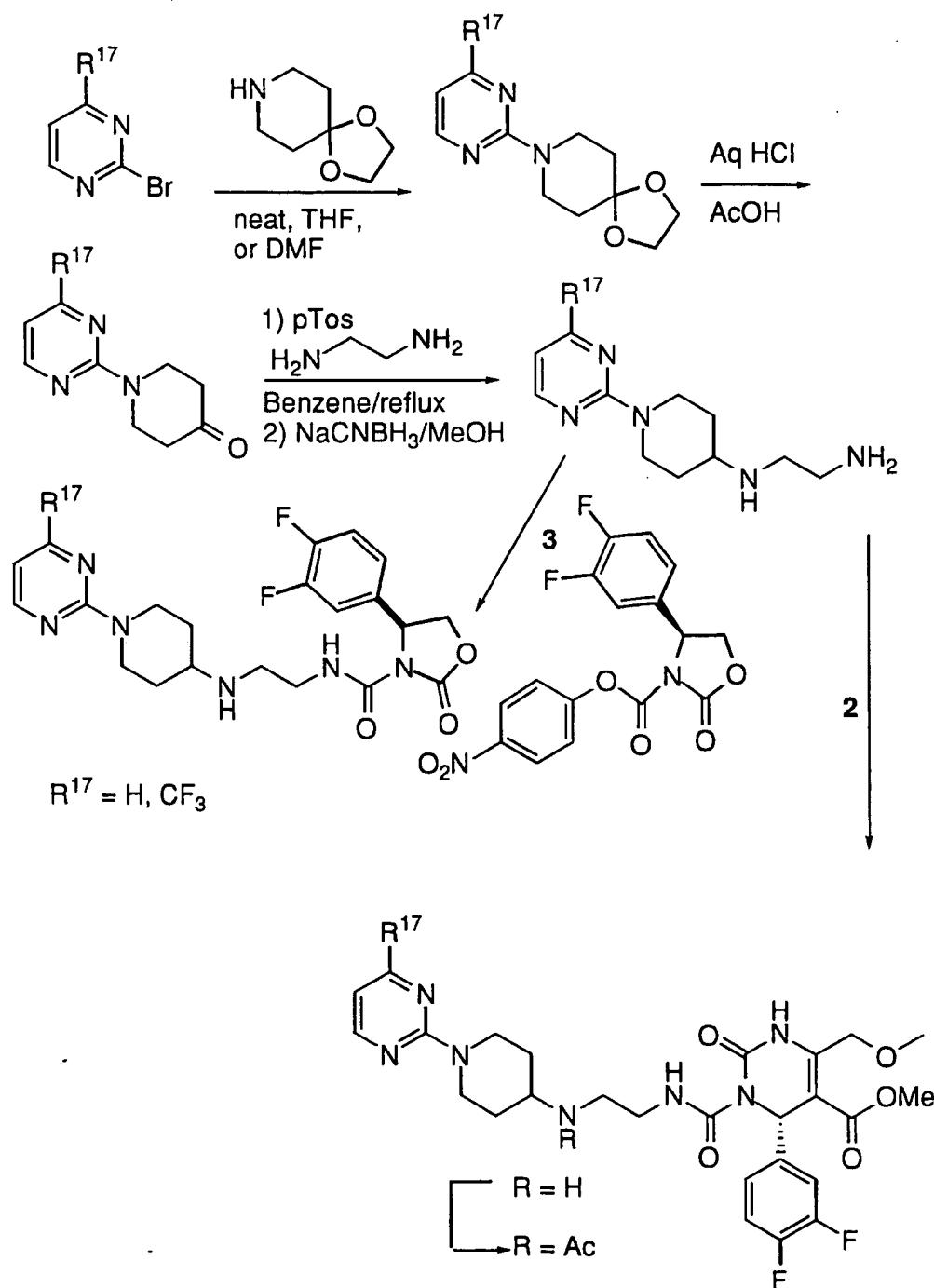


SCHEME 2

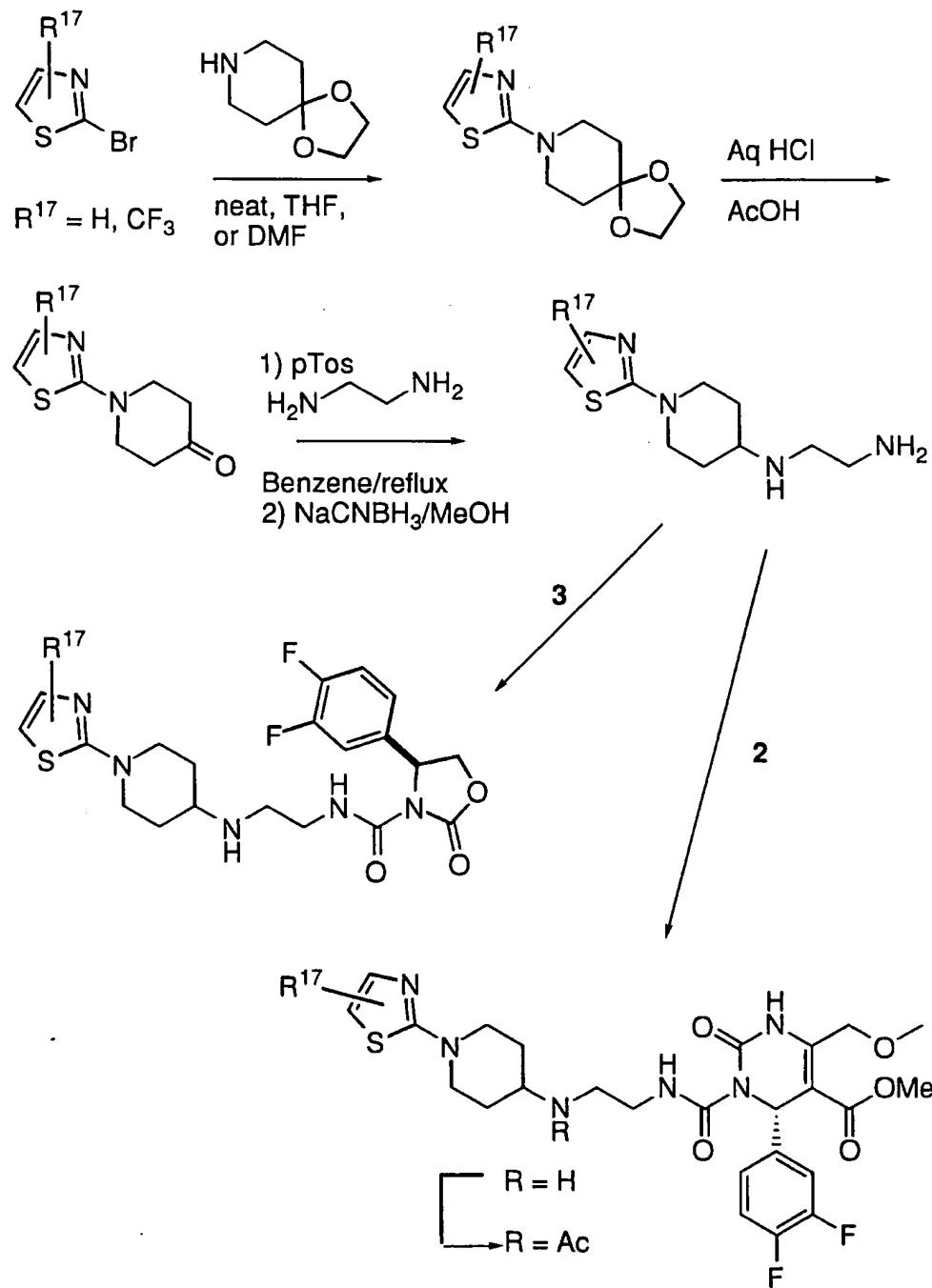


Similarly, heteroaryl variants are synthesized as shown in
5 Schemes 3A and 3B.

SCHEME 3A

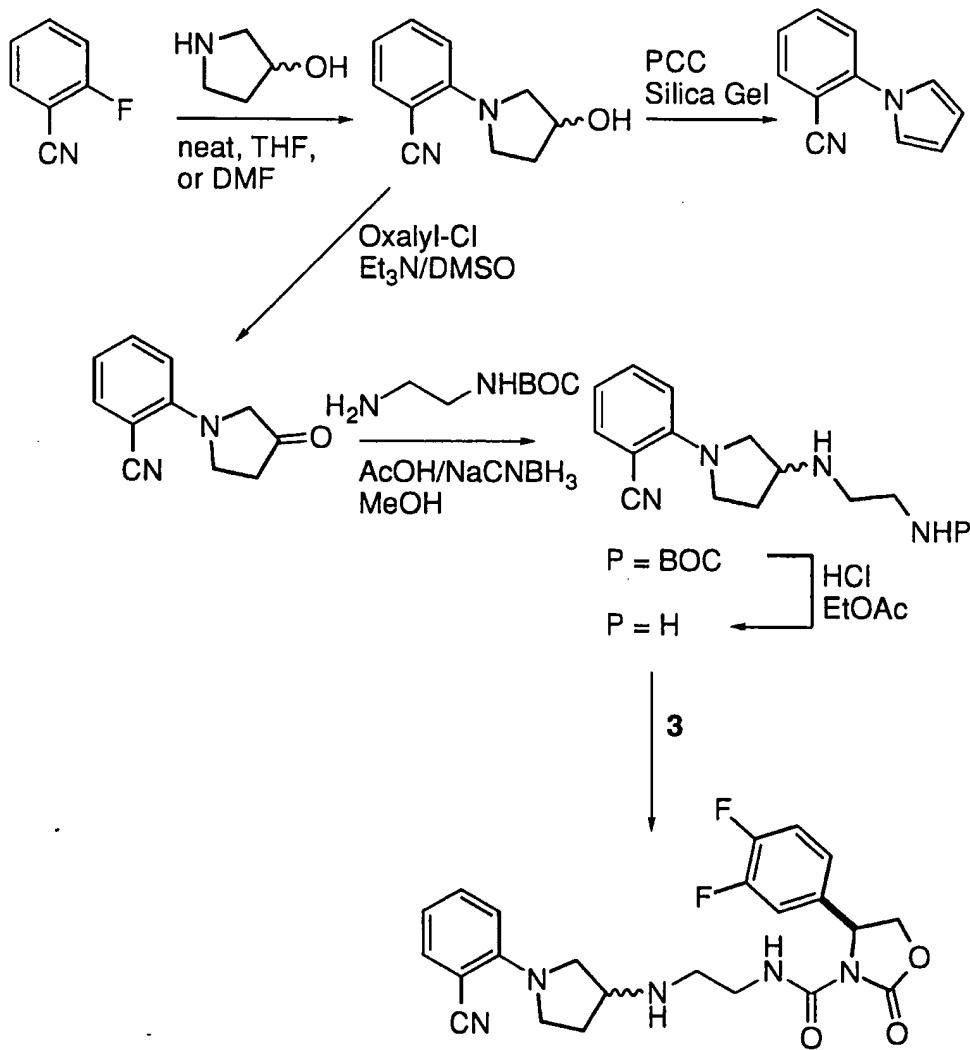


SCHEME 3B

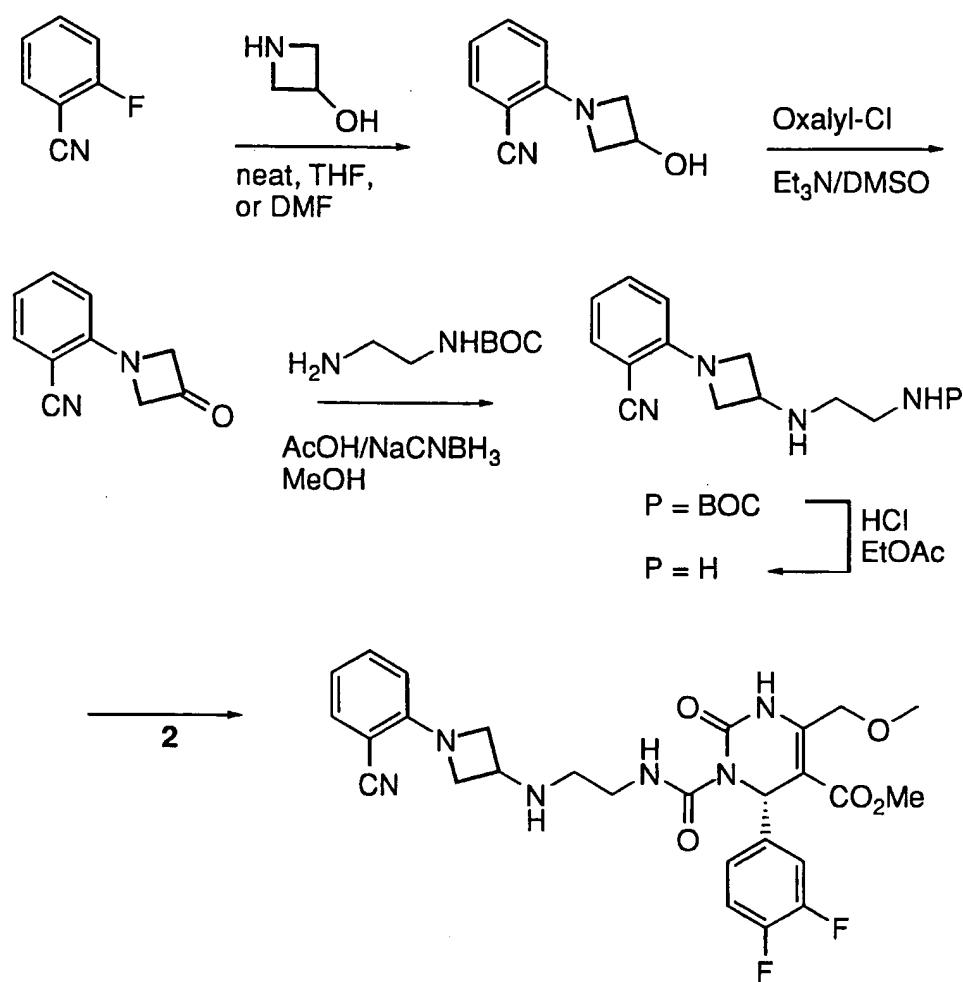


Pyrrolidinyl and azetidinyl analogs are prepared as shown in Schemes 4 and 5. Addition of 3-hydroxypyrrolidine to, for instance, 2-fluorobenzonitrile, followed by Swern oxidation provided the required N-aryl-3-oxopyrrolidine. Reductive amination with mono N-Boc ethylenediamine, followed by, HCl-EtOAc protection and selective acylation provided the representative example as shown in Scheme 4. The azetidinyl analog was prepared in analogous fashion starting from 3-hydroxy azetidine as shown in Scheme 5.

SCHEME 4



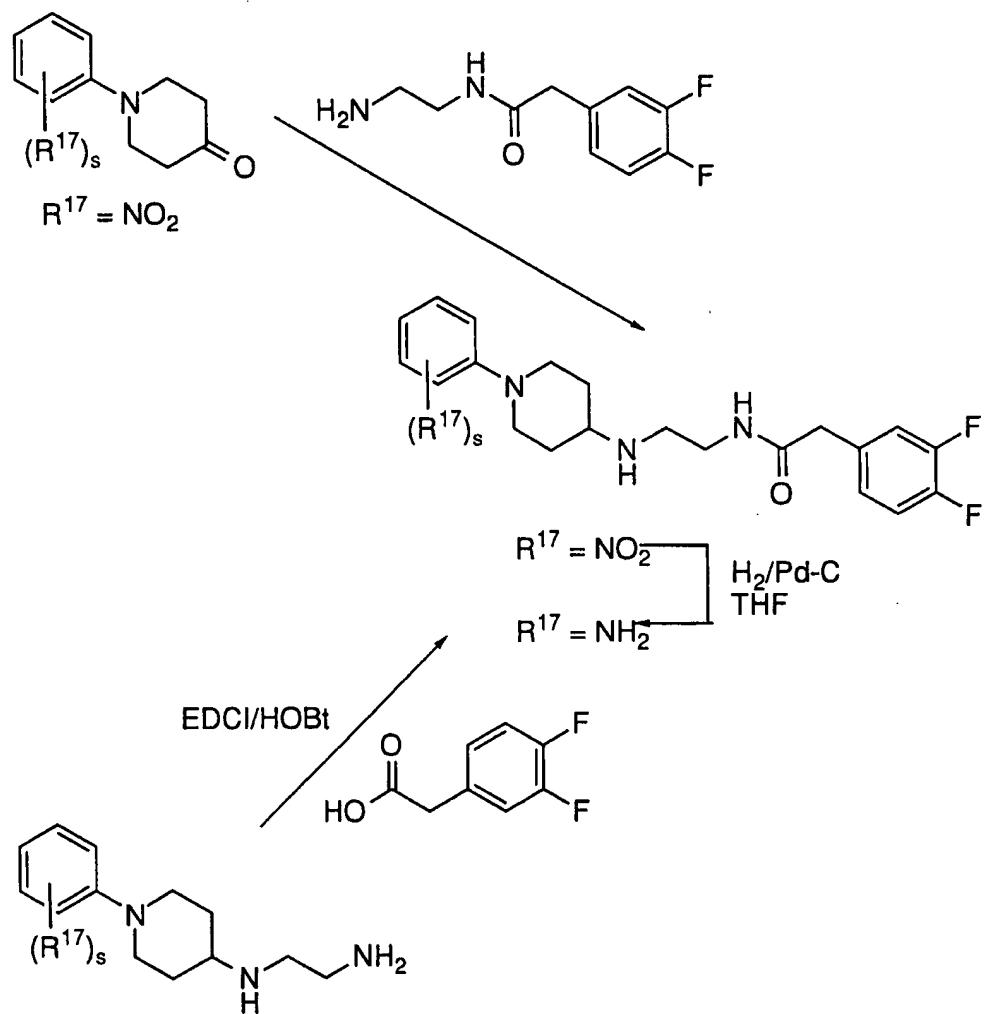
SCHEME 5



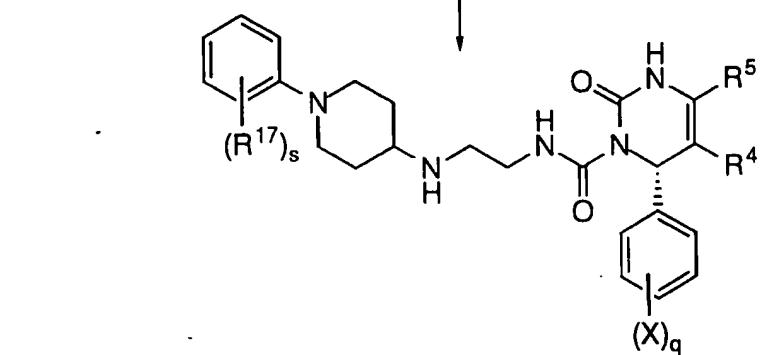
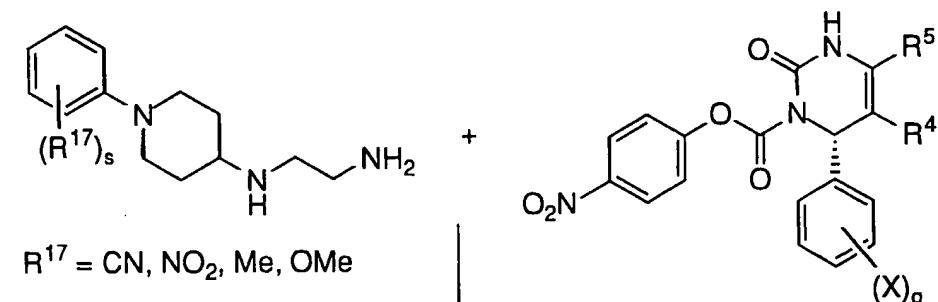
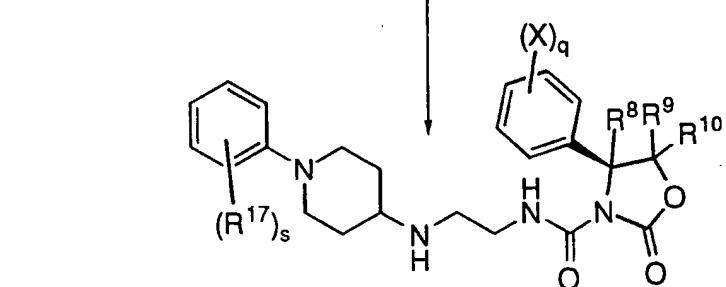
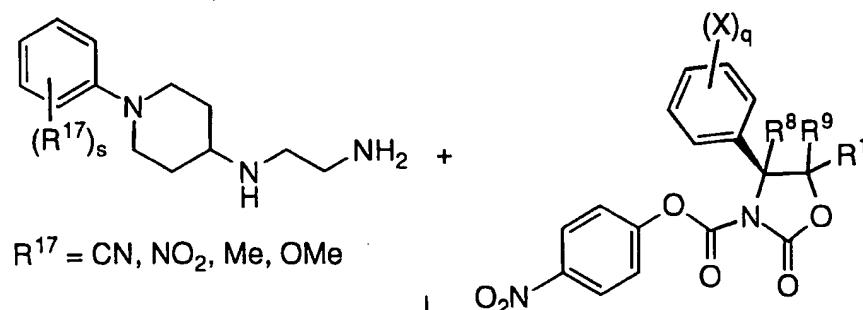
5

Additional analogs are prepared utilizing the procedures of Schemes 6-9.

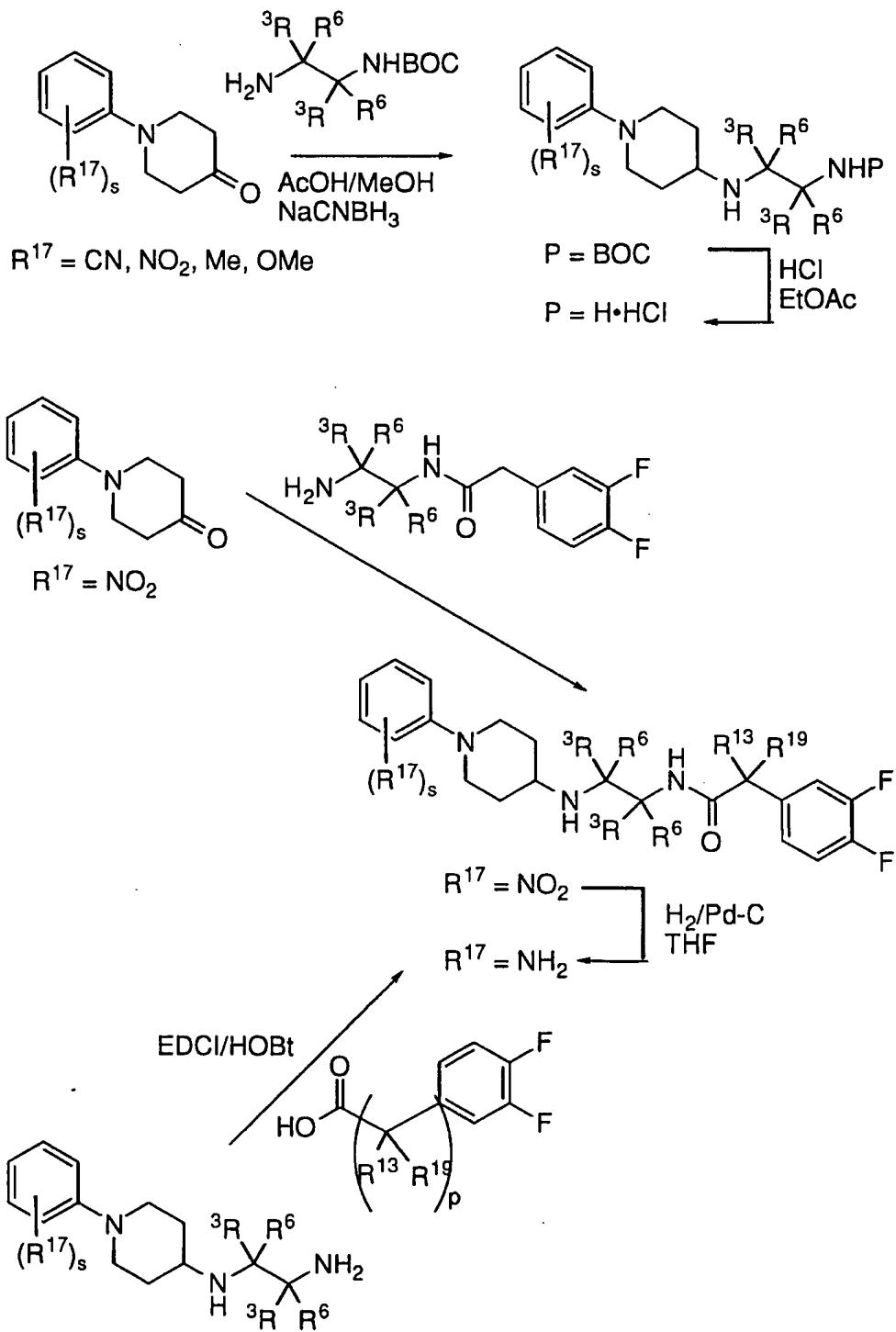
SCHEME 6



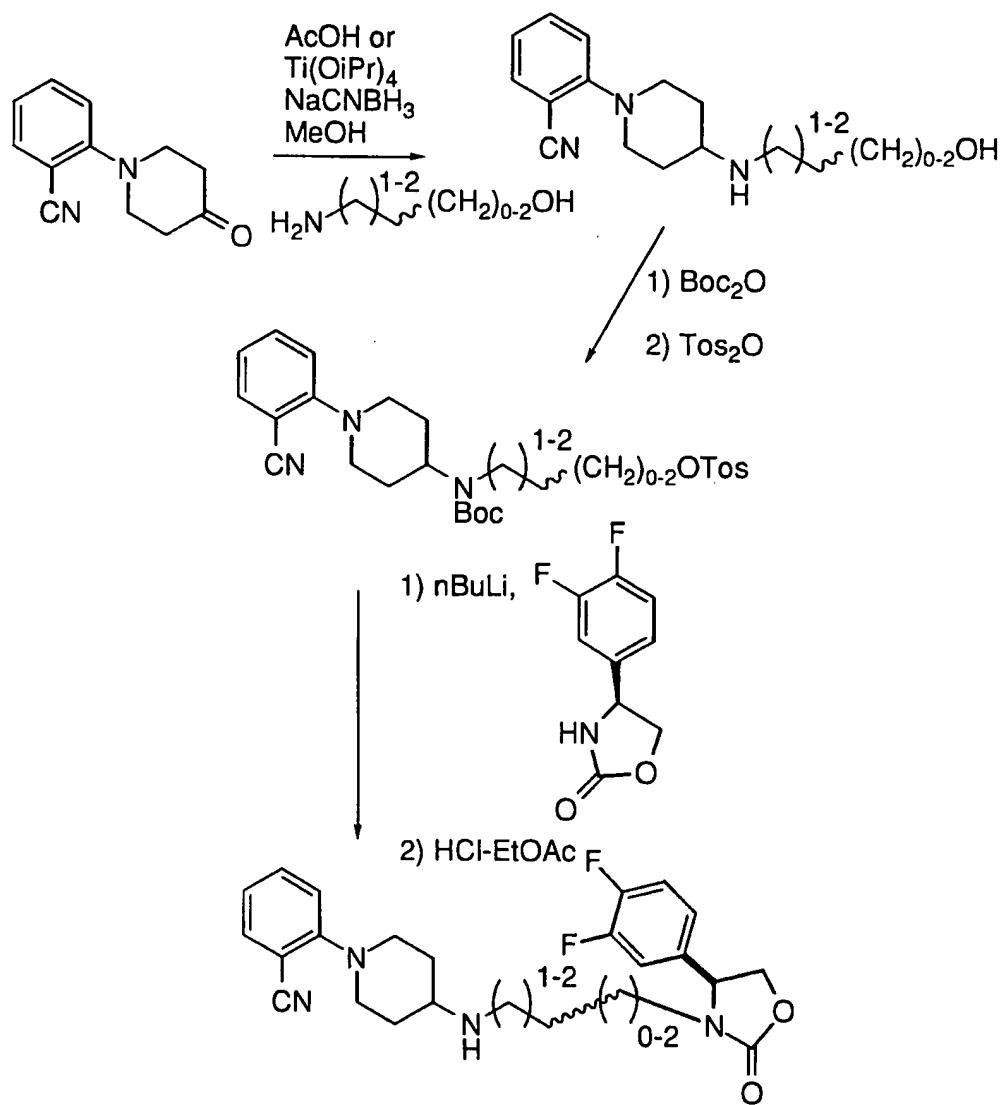
SCHEME 7



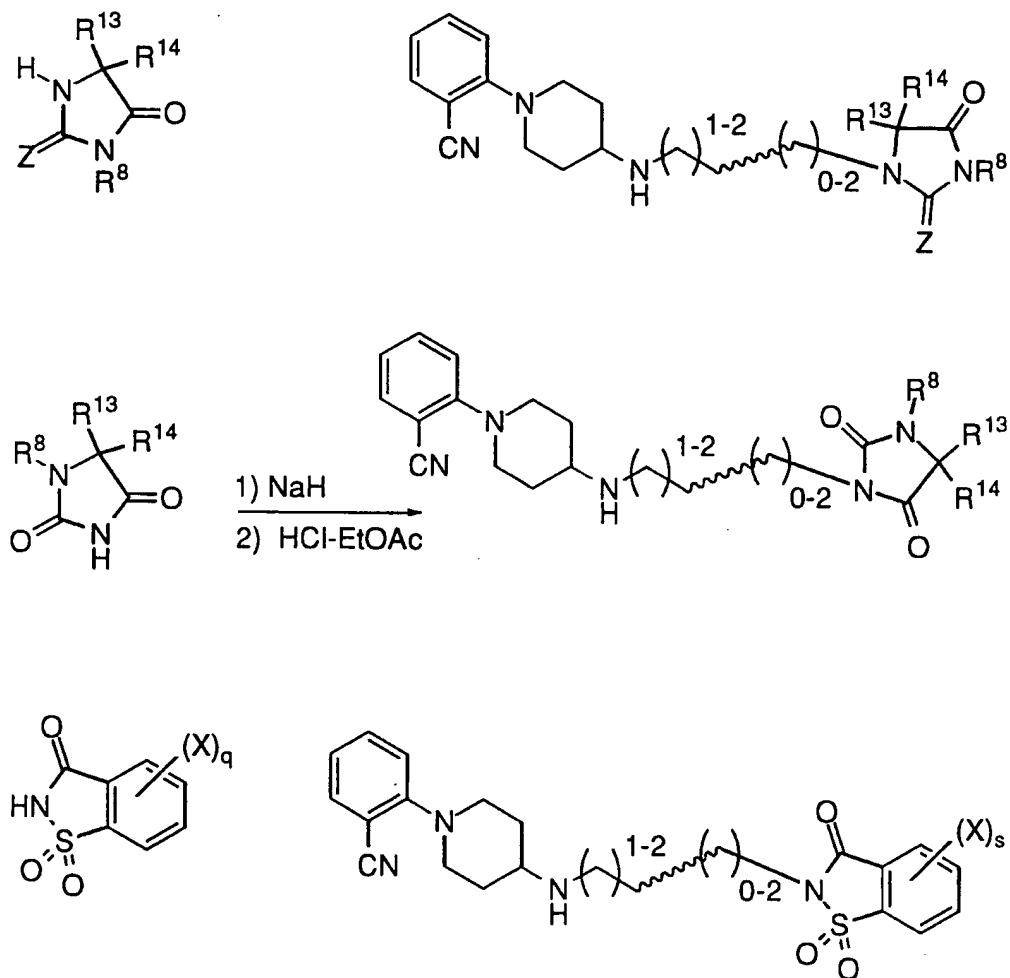
SCHEME 8



SCHEME 9



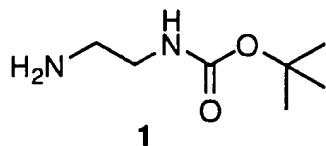
SCHEME 9 (CONT'D)



5

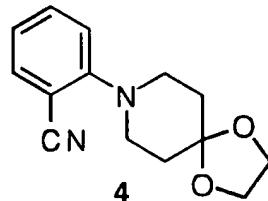
The following examples are provided to further define the invention without, however, limiting the invention to the particulars of these examples.

EXAMPLE 1

*tert*-Butyl *N*-(2-aminoethyl)carbamate (1)

A solution of ethylenediamine (39.8 g, 0.663 mole) in THF (1 L) was cooled to 0 °C and treated with a solution of di-*tert*-butyldicarbonate (22.2 g, 0.101 mole) in THF (500 mL) dropwise over 6h. The resulting mixture was stirred at room temperature overnight. The solvent was removed in vacuo and the residue dissolved in ethyl acetate and brine. The organic layer was washed with two additional portions of brine and dried over Na₂SO₄. The solvent was removed in vacuo to afford the title compound (1) as a pale yellow liquid.

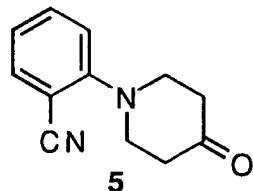
EXAMPLE 2

*N*-(2-Cyanophenyl)-4-piperidone ethylene ketal (4)

A solution of 2-fluorobenzonitrile (2.75 g, 22.7 mmol) and 4-piperidone ethylene ketal (4.25 g, 29.7 mmol) in DMF (40 mL) was heated to 120 °C for 4 h. The resulting mixture was cooled to room temperature overnight. The solvent was removed in vacuo and the residue dissolved in ether and sodium bicarbonate solution. The aqueous layer was extracted with two additional portions of ether and the combined organic extracts were washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure to afford the title compound (4). The crude product was used directly.

25

EXAMPLE 3

*N*-(2-Cyanophenyl)-4-piperidone (5)

5 A solution of 4 (533 mg, 2.18 mmol) in ether (10 mL) was treated with 5% aqueous HCl (20 mL). The mixture was stirred at room temperature (11 d). The reaction was diluted with ether and neutralized with sodium bicarbonate solution. The aqueous layer was extracted with two additional portions of ether and the combined organic extracts were washed with brine, dried over Na_2SO_4 , and concentrated under reduced pressure. PCTLC (SiO_2 , 4mm, 20% EtOAc-80% hexane) afforded the title compound (5).

10

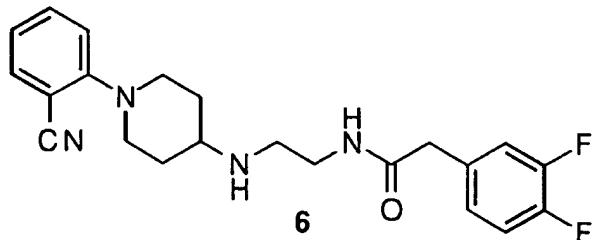
^1H NMR (CDCl_3 , 400 MHz) consistent with assigned structure.

15 FABLRMS m/e 201 g/mole (M^++H , $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O} = 201$ g/mole.)

HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H_2O [0.1% H_3PO_4] - CH_3CN , 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) RT = 7.32 min; focus = 215 nm; 97.5% pure.

20

EXAMPLE 4

*N*-(2-(1-(2-Cyanophenyl)piperidin-4-ylamino)ethyl)-2-(3,4-difluorophenyl)acetamide (6)

A solution of 5 (190 mg, 0.94 mmol), N-(2-aminoethyl)-1-(3,4-difluorophenyl)acetamide (120 mg, 0.56 mmol), and acetic acid (168 mg, 2.79 mmol) in methanol (2 mL) was treated with sodium cyanoborohydride (35 mg, 0.56 mmol) at room temperature. The 5 resulting mixture was stirred at room temperature (30 min). The solvent was removed in vacuo and the residue dissolved in dichloromethane and sodium bicarbonate solution. The aqueous layer was extracted with two additional portions of dichloromethane and the combined organic extracts were washed with brine, dried over Na_2SO_4 , 10 and concentrated under reduced pressure. PCTLC (SiO_2 , 4mm, 10% EtOH-90% CHCl_3) afforded the title compound (6) which was converted to the hydrochloride salt after treatment with methanolic HCl.

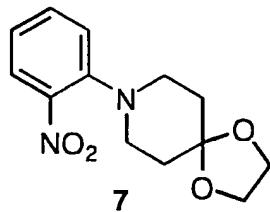
15 ^1H NMR (CDCl_3 , 400 MHz) consistent with assigned structure.

15 FABLRMS m/e 399 g/mole (M^++H , $\text{C}_{22}\text{H}_{24}\text{F}_2\text{N}_4\text{O} = 399$ g/mole.)

15 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H_2O [0.1% H_3PO_4] - CH_3CN , 95% - 5%, 5% - 95%, over 16 minutes, 2 mL/min flow rate) RT = 7.97 min; focus = 215 nm; 98.5% pure.

20

EXAMPLE 5



N-(2-Nitrophenyl)-4-piperidone ethylene ketal (7)

25 A solution of 1-fluoro-2-nitrobenzene (5.80 g, 41.1 mmol) and 4-piperidone ethylene ketal (6.68 g, 46.6 mmol) in THF (100 mL) was stirred at room temperature (2 h). The resulting mixture was washed with water and sodium bicarbonate solution. The aqueous layer was extracted with two portions of ethyl acetate and the combined organic extracts were washed with brine, dried over Na_2SO_4 , and concentrated

under reduced pressure. Flash chromatography on silica gel (10% ethyl acetate / hexane) afforded the title compound (7).

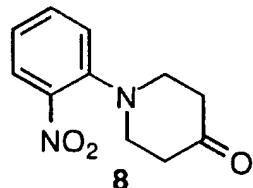
1H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

5 FABLRMS m/e 265 g/mole (M⁺+H, C₁₃H₁₆N₂O₄ = 265 g/mole.)

HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) RT = 9.12 min; focus = 215 nm; 100% pure.

10

EXAMPLE 6



N-(2-Nitrophenyl)-4-piperidone (8)

15 A solution of 7 (7.44 g, 28.1 mmol) in ether (300 mL) was treated with 5% aqueous HCl (150 mL). The mixture was stirred at room temperature (5 d). The reaction was quenched with solid sodium bicarbonate. The aqueous layer was extracted with three additional portions of ether and the combined organic extracts were washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure.

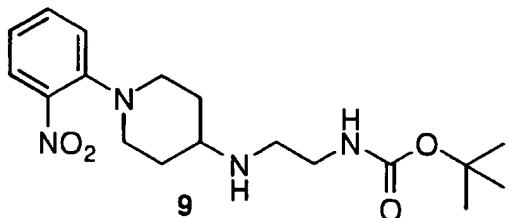
20 Flash chromatography on silica gel (20% ethyl acetate / hexane) afforded the title compound (8).

1H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

25 FABLRMS m/e 221 g/mole (M⁺+H, C₁₁H₁₂N₂O₃ = 221 g/mole.)

HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) RT = 7.81 min; focus = 215 nm; 100% pure.

EXAMPLE 7



(2-(1-(2-Nitro-phenyl)-piperidin-4-ylamino)-ethyl)-carbamic acid *tert*-butyl ester (9)

5 A solution of 8 (945 mg, 4.29 mmol), 1 (695 mg, 4.33 mmol), and acetic acid (1.31 g, 21.8 mmol) in methanol (10 mL) was treated with sodium cyanoborohydride (270 mg, 4.29 mmol) at room temperature. The resulting mixture was stirred at room temperature overnight. The solvent was removed in vacuo and the residue dissolved in

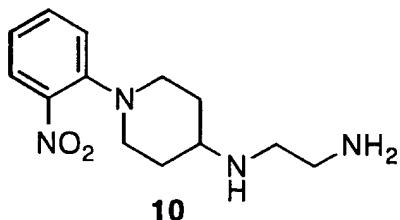
10 dichloromethane and sodium bicarbonate solution. The aqueous layer was extracted with two additional portions of dichloromethane and the combined organic extracts were washed with brine, dried over Na_2SO_4 , and concentrated under reduced pressure. PCTLC (SiO_2 , 6mm, 10% EtOH-90% CHCl_3) afforded the title compound (9).

15 ^1H NMR (CDCl_3 , 400 MHz) consistent with assigned structure.

FABLRMS m/e 365 g/mole (M^++H , $\text{C}_{18}\text{H}_{28}\text{N}_4\text{O}_4 = 365$ g/mole.)

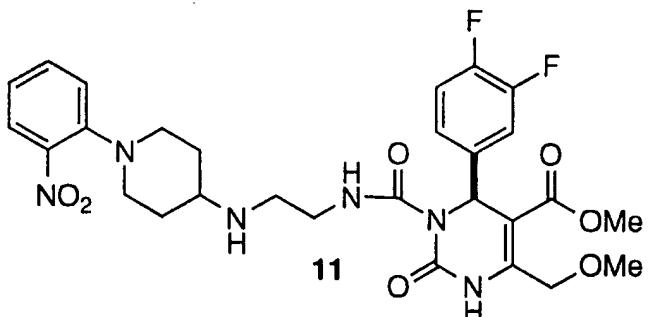
20 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H_2O [0.1% H_3PO_4] - CH_3CN , 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) RT = 7.90 min; focus = 215 nm; 99% pure.

EXAMPLE 8

N1-(1-(2-Nitrophenyl)piperidin-4-yl)ethane-1,2-diamine (10)

A solution of 9 (576 mg, 1.66 mmol) in ethyl acetate (50 mL) 5 was cooled to 0°C and treated with anhydrous HCl (5 min). The mixture was stirred at room temperature (2h). The solvent was removed in vacuo and the residue dissolved in dichloromethane and sodium carbonate solution. The aqueous layer was extracted with two additional portions of dichloromethane. The combined organic extracts were 10 washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure to afford the title compound (10). The crude product was used directly.

EXAMPLE 9



15

(4S)-4-(3,4-Difluorophenyl)-6-methoxymethyl-3-(2-(1-(2-nitrophenyl)piperidin-4-ylamino)ethylcarbamoyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester (11)

A solution of 2 (53 mg, 0.11 mmol) in dichloromethane (1 20 mL) was treated with a solution of 10 (35 mg, 0.13 mmol) in dichloromethane (1 mL) at room temperature. The mixture was stirred

at room temperature (30 min). The mixture was diluted with sodium carbonate solution and the aqueous layer was extracted with two additional portions of dichloromethane. The combined organic extracts were washed with brine and dried over Na_2SO_4 . The solvent was removed in vacuo. PCTLC (SiO_2 , 2mm, 1% NH_4OEt -10% EtOH-90% CHCl_3) afforded the title compound (11) which was converted to the hydrochloride salt after treatment with methanolic HCl.

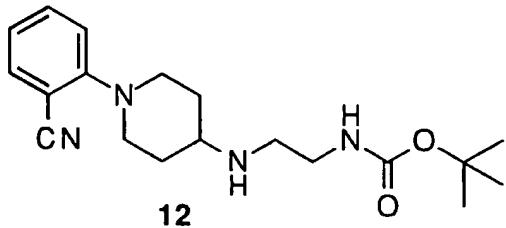
5 ^1H NMR (CDCl_3 , 400 MHz) consistent with assigned structure.

10 FABLRMS m/e 603 g/mole (M^++H , $\text{C}_{28}\text{H}_{32}\text{F}_2\text{N}_6\text{O}_7 = 603$ g/mole.)

15 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H_2O [0.1% H_3PO_4] - CH_3CN , 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) RT = 9.53 min; focus = 215 nm; 100% pure.

15

EXAMPLE 10



(2-(1-(2-Cyanophenyl)piperidin-4-ylamino)ethyl)carbamic acid tert-butyl ester (12)

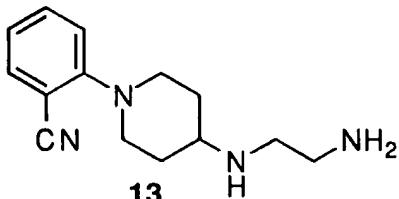
20 A solution of 5 (200 mg, 1.00 mmol), 1 (161 mg, 1.00 mmol), and acetic acid (300 mg, 5.00 mmol) in methanol (2 mL) was treated with sodium cyanoborohydride (66 mg, 1.05 mmol) at room temperature. The resulting mixture was stirred at room temperature overnight. The solvent was removed in vacuo and the residue dissolved in dichloromethane and sodium bicarbonate solution. The aqueous layer was extracted with three additional portions of dichloromethane and the combined organic extracts were washed with brine, dried over Na_2SO_4 , and concentrated under reduced pressure. PCTLC (SiO_2 , 4mm, 10% EtOH-90% CHCl_3) afforded the title compound (12).

¹H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

FABLRMS m/e 345 g/mole (M⁺+H, C₁₉H₂₈N₄O₂ = 345 g/mole.)

5 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) RT = 7.66 min; focus = 215 nm; 92% pure.

EXAMPLE 11



10

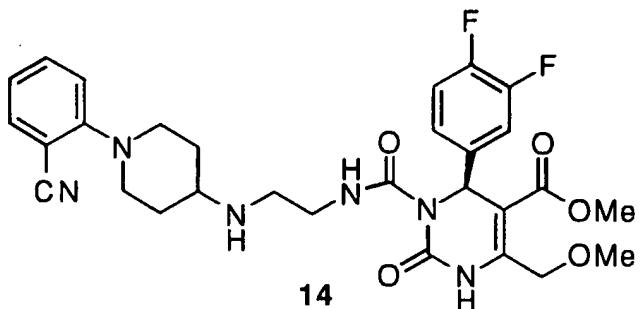
2-(4-(2-Aminoethylamino)piperidin-1-yl)benzonitrile (13)

A solution of 12 (256 mg, 0.74 mmol) in ethyl acetate (50 mL) was cooled to 0°C and treated with anhydrous HCl (1 min). The mixture was stirred at room temperature (1 h). The solvent was removed in vacuo and the residue dissolved in dichloromethane and sodium carbonate solution. The aqueous layer was extracted with two additional portions of dichloromethane. The combined organic extracts were washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure to afford the title compound (13). The crude product was used directly.

20 FABLRMS m/e 245 g/mole (M⁺+H, C₁₄H₂₀N₄ = 245 g/mole.)
 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) RT = 5.15 min; focus = 215 nm; 93.5% pure.

25

EXAMPLE 12



(4S)-3-(2-(1-(2-Cyanophenyl)piperidin-4-ylamino)ethylcarbamoyl)-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-

5 carboxylic acid methyl ester (14)

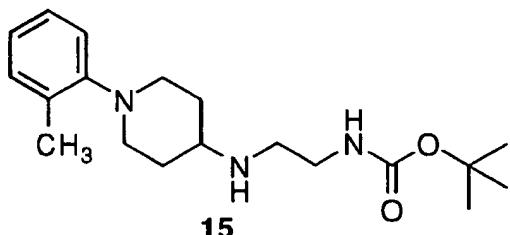
A solution of 2 (77 mg, 0.16 mmol) in dichloromethane (1 mL) was treated with a solution of 13 (50 mg, 0.20 mmol) in dichloromethane (1 mL) at room temperature. The mixture was stirred at room temperature (1 h). The mixture was diluted with sodium carbonate solution and the aqueous layer was extracted with two additional portions of dichloromethane. The combined organic extracts were washed with brine and dried over Na_2SO_4 . The solvent was removed in vacuo. PCTLC (SiO_2 , 2mm, 1% NH_4OEt -10% EtOH-90% CHCl_3) afforded the title compound (14) which was converted to the hydrochloride salt after treatment with methanolic HCl.

10 ^1H NMR (CDCl_3 , 400 MHz) consistent with assigned structure.

15 FABLRMS m/e 583 g/mole (M^++H , $\text{C}_{29}\text{H}_{32}\text{F}_2\text{N}_6\text{O}_5 = 583$ g/mole.)

20 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H_2O [0.1% H_3PO_4] - CH_3CN , 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) RT = 9.34 min; focus = 215 nm; 100% pure.

EXAMPLE 13

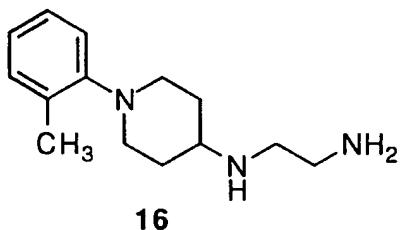


(2-(1-o-Tolyl-piperidin-4-ylamino)-ethyl)-carbamic acid *tert*-butyl ester (15)

5 Following the procedure of Example 7, but using N-o-tolyl-4-piperidone in place of N-(2-nitrophenyl)-4-piperidone, the crude compound was obtained. PCTLC (SiO_2 , 2mm, 10% EtOH-90% CHCl_3) afforded the title compound (15).

10 FABLRMS m/e 334 g/mole (M^++H , $\text{C}_{19}\text{H}_{31}\text{N}_3\text{O}_2 = 334$ g/mole.)

EXAMPLE 14



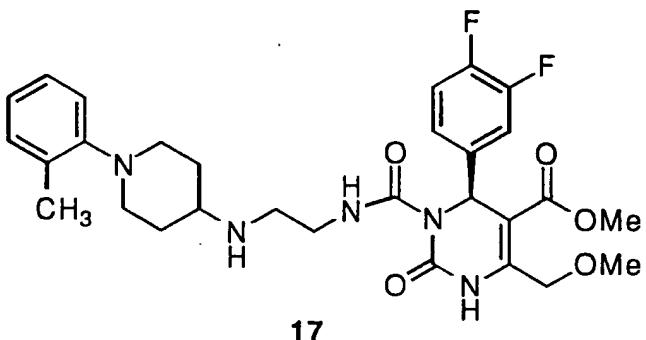
N1-(1-o-Tolylpiperidin-4-yl)ethane-1,2-diamine (16)

15 A solution of 15 (115 mg, 0.344 mmol) in ethyl acetate (2 mL) was treated with sat'd HCl/EtOAc solution (3 mL) at room temperature. The mixture was stirred at room temperature (1 h). The solvent was removed in vacuo and the residue dissolved in dichloromethane and sodium carbonate solution. The aqueous layer was extracted with two additional portions of dichloromethane and the combined organic extracts were washed with brine, dried over Na_2SO_4 , and concentrated under reduced pressure to afford the title compound (16). The crude product was used directly.

HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) RT = 4.82 min; focus = 215 nm; 98.5% pure.

5

EXAMPLE 15



(4S)-4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(1-o-tolylpiperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid methyl ester (17)

10 A solution of 16 (51 mg, 0.218 mmol) in dichloromethane (1 mL) was treated with solid 2 (88 mg, 0.184 mmol) at room temperature. The mixture was stirred at room temperature (30 min). The mixture was diluted with sodium carbonate solution and the aqueous layer was extracted with two additional portions of dichloromethane. The

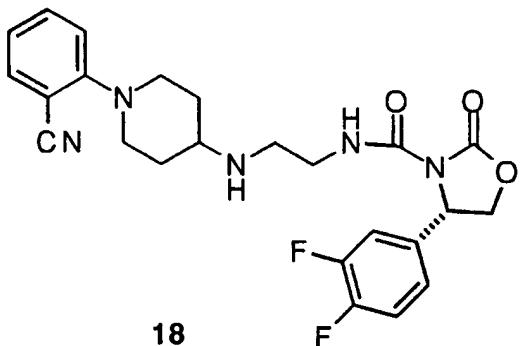
15 combined organic extracts were washed with brine and dried over Na₂SO₄. The solvent was removed in vacuo. PCTLC (SiO₂, 2mm, 1% NH₄OEt-10% EtOH-90% CHCl₃) afforded the title compound (17) which was converted to the hydrochloride salt after treatment with methanolic HCl.

20 ¹H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

FABLRMS m/e 572 g/mole (M⁺+H, C₂₉H₃₅F₂N₅O₅ = 572 g/mole.)

25 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) RT = 9.11 min; focus = 215 nm; 100% pure.

EXAMPLE 16



5 (4S)-4-(3,4-Difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid (2-(1-(2-cyanophenyl)piperidin-4-ylamino)ethyl)amide (18)

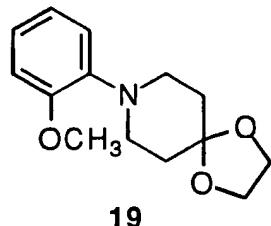
A solution of 13 (61 mg, 0.249 mmol) in dichloromethane (2 mL) was treated with solid 3 (66 mg, 0.181 mmol) at room temperature. The mixture was stirred at room temperature overnight. The mixture was diluted with sodium carbonate solution and the aqueous layer was extracted with two additional portions of dichloromethane. The combined organic extracts were washed with brine and dried over Na_2SO_4 . The solvent was removed in vacuo. PCTLC (SiO_2 , 2mm, 10% EtOH-90% CHCl_3) afforded the title compound (18) which was converted to the hydrochloride salt after treatment with methanolic HCl.

15 ^1H NMR (CDCl_3 , 400 MHz) consistent with assigned structure.

FABLRMS m/e 470 g/mole (M^++H , $\text{C}_{24}\text{H}_{25}\text{F}_2\text{N}_5\text{O}_3 = 470$ g/mole.)

20 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H_2O [0.1% H_3PO_4] - CH_3CN , 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) RT = 8.31 min; focus = 215 nm; 97% pure. Anal. Calcd for $\text{C}_{24}\text{H}_{25}\text{F}_2\text{N}_5\text{O}_3 \bullet 0.90 \text{ HCl} \bullet 0.40 \text{ H}_2\text{O}$: C = 56.08, H = 5.33, N = 13.63. Found: C = 56.13, H = 5.34, N = 13.24.

EXAMPLE 17



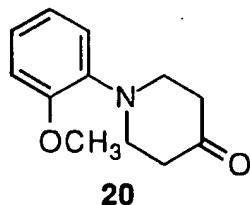
19

N-(2-Methoxyphenyl)-4-piperidone ethylene ketal (19)

A solution of 2-bromoanisole (6.00 g, 32.08 mmol) and 4-5 piperidone ethylene ketal (5.54 g, 38.69 mmol) in toluene (250 mL) was treated with sodium tert-butoxide (4.40 g, 45.76 mmol), tri-*o*-tolylphosphine (411 mg, 1.35 mmol), and tris(dibenzylideneacetone)dipalladium(0) (295 mg, 0.32 mmol) at room temperature. The mixture was heated in an oil bath (100 °C, 2 h). The 10 mixture was diluted with ether and the organics washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. Flash chromatography on silica gel (20% ethyl acetate / hexane) afforded the title compound (19).

15

EXAMPLE 18



20

N-(2-Methoxyphenyl)-4-piperidone (20)

A solution of 19 (570 mg, 2.28 mmol) in acetic acid (20 mL), water (20 mL), and concentrated HCl (5 mL) was heated in an oil bath (50 °C) overnight. The solvent was removed in vacuo and the residue 20 dissolved in ether and sodium carbonate solution. The aqueous layer was extracted with two additional portions of ether and the combined organic extracts were washed with brine, dried over Na₂SO₄, and

concentrated under reduced pressure. PCTLC (SiO₂, 2mm, CHCl₃) afforded the title compound (20)

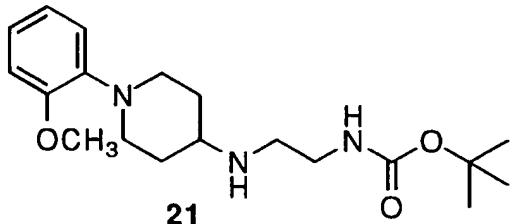
1H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

5 FABLRMS m/e 206 g/mole (M⁺⁺H, C₁₂H₁₅NO₂ = 206 g/mole.)

HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) RT = 3.07 min; focus = 215 nm; 99% pure.

10

EXAMPLE 19



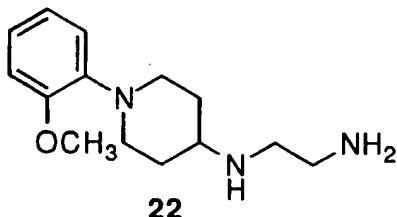
(2-(1-(2-Methoxyphenyl)piperidin-4-ylamino)-ethyl)carbamic acid tert-butyl ester (21)

15 A solution of 20 (186 mg, 0.906 mmol), 1 (153 mg, 0.955 mmol), and acetic acid (288 mg, 4.80 mmol) in methanol (1 mL) was treated with sodium cyanoborohydride (63 mg, 1.00 mmol) at room temperature. The resulting mixture was stirred at room temperature (2 h). The solvent was removed in vacuo and the residue dissolved in 20 dichloromethane and sodium bicarbonate solution. The aqueous layer was extracted with two additional portions of dichloromethane and the combined organic extracts were washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. PCTLC (SiO₂, 2mm, 10% EtOH; 90% CHCl₃) afforded the title compound (21).

25 1H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

FABLRMS m/e 350 g/mole (M⁺⁺H, C₁₉H₃₁N₃O₃ = 350 g/mole.)

EXAMPLE 20

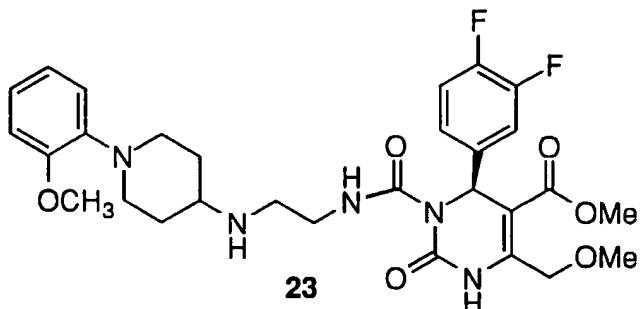
N1-(1-(2-Methoxyphenyl)piperidin-4-yl)ethane-1,2-diamine (22)

5 Following the procedure of Example 14, but using (21) in place of (15), the title compound (22) was obtained. The crude product was used directly.

FABLRMS m/e 250 g/mole (M^++H , $C_{14}H_{23}N_3O = 250$ g/mole.)

10 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H_2O [0.1% H_3PO_4] - CH_3CN , 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) RT = 3.60 min; focus = 215 nm; 100% pure.

EXAMPLE 21



15

(4S)-4-(3,4-Difluorophenyl)-6-methoxymethyl-3-(2-(1-(2-methoxyphenyl)piperidin-4-ylamino)ethylcarbamoyl)-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid methyl ester (23)

20 Following the procedure of Example 15, but using (22) in place of (16), the crude product (23) was obtained. PCTLC (SiO_2 , 2mm, 10% $EtOH$ -90% $CHCl_3$) afforded the title compound (23) which was converted to the hydrochloride salt after treatment with methanolic HCl .

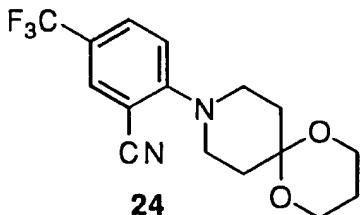
¹H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

FABLRMS m/e 588 g/mole (M⁺+H, C₂₉H₃₅F₂N₅O₆ = 588 g/mole.)

5 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) RT = 7.70 min; focus = 215 nm; 96.3% pure.
Anal. Calcd for C₂₉H₃₅F₂N₅O₆ • 2.00 HCl • 0.50 H₂O: C = 52.02, H = 5.72, N = 10.46. Found: C = 52.04, H = 5.78, N = 10.30.

10

EXAMPLE 22



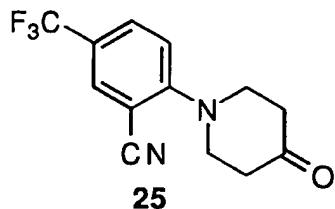
N-(2-Cyano-4-trifluoromethylphenyl)-4-piperidone propylene ketal (24)

15 A solution of 2-fluoro-5-trifluoromethylbenzonitrile (2.01 g, 10.61 mmol) and 4-piperidone propylene ketal (1.71 g, 10.9 mmol) in THF (10 mL) was stirred at room temperature (1 h). The resulting mixture was diluted with ether and sodium carbonate solution. The aqueous layer was extracted with two portions of ether and the combined organic extracts were washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure to afford the title compound (24).

20 FABLRMS m/e 327 g/mole (M⁺+H, C₁₆H₁₇F₃N₂O₂ = 327 g/mole.)

25 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) RT = 11.04 min; focus = 255 nm; 97.2% pure.

EXAMPLE 23

N-(2-Cyano-4-trifluoromethylphenyl)-4-piperidone (25)

A solution of 24 (1.70 g, 5.20 mmol) in ether (20 mL) was
 5 treated with 6N aqueous HCl (50 mL). The mixture was stirred at room
 temperature (20 min). The reaction mixture was neutralized with
 sodium carbonate solution and solid sodium hydroxide. The aqueous
 layer was extracted with two additional portions of ether and the
 combined organic extracts were washed with brine, dried over Na_2SO_4 ,
 10 and concentrated under reduced pressure. PCTLC (SiO_2 , 6mm, 10%
 EtOH-90% CHCl_3) afforded the title compound (25).

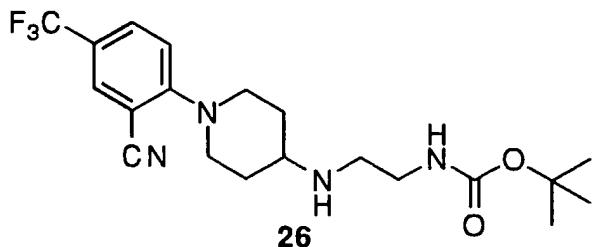
^1H NMR (CDCl_3 , 400 MHz) consistent with assigned
 structure.

FABLRMS m/e 269 g/mole (M^++H , $\text{C}_{13}\text{H}_{11}\text{F}_3\text{N}_2\text{O} = 269$
 15 g/mole.)

HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm;
 gradient = H_2O [0.1% H_3PO_4] - CH_3CN , 95% - 5%, 5% - 95%, over 16
 minutes, 2 ml/min flow rate) RT = 9.35 min; focus = 215 nm; 98.9% pure.

20

EXAMPLE 24

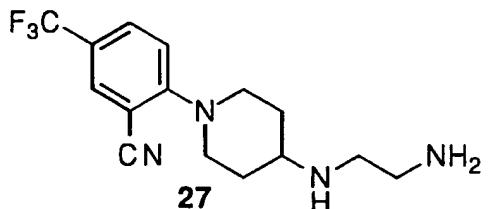
(2-(1-(2-Cyano-4-trifluoromethylphenyl)piperidin-4-ylamino)-ethyl)carbamic acid tert-butyl ester (26)

A solution of 25 (535 mg, 1.99 mmol), 1 (335 mg, 2.09 mmol), and acetic acid (629 mg, 10.48 mmol) in methanol(2 mL)/dichloroethane(1 mL) was treated with sodium cyanoborohydride (130 mg, 2.06 mmol) at room temperature. The resulting mixture was 5 stirred at room temperature overnight. The solvent was removed in vacuo and the residue dissolved in dichloromethane and sodium carbonate solution. The aqueous layer was extracted with two additional portions of dichloromethane and the combined organic extracts were washed with brine, dried over Na_2SO_4 , and concentrated under reduced 10 pressure. PCTLC (SiO_2 , 4mm, 10% EtOH-90% CHCl_3) afforded the title compound (26).

HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H_2O [0.1% H_3PO_4] - CH_3CN , 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) RT = 9.16 min; focus = 215 nm; 100% pure.

15

EXAMPLE 25



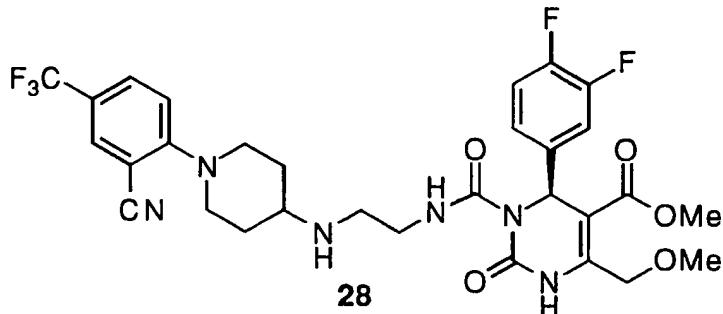
2-(4-(2-Aminoethylamino)piperidin-1-yl)-5-trifluoromethylbenzonitrile (27)

20 Following the procedure of Example 14, but using (26) in place of (15), the title compound (27) was obtained.

FABLRMS m/e 313 g/mole (M^++H , $\text{C}_{15}\text{H}_{19}\text{F}_3\text{N} = 313$ g/mole.)

25 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H_2O [0.1% H_3PO_4] - CH_3CN , 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) RT = 6.81 min; focus = 215 nm; 95.2% pure.

EXAMPLE 26



(4S)-3-(2-(1-(2-Cyano-4-trifluoromethylphenyl)piperidin-4-ylamino)-ethylcarbamoyl)-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-1,2,3,4-

5 tetrahydropyrimidine-5-carboxylic acid methyl ester (28)

Following the procedure of Example 15, but using (27) in place of (16), the crude product was obtained. PCTLC (SiO_2 , 2mm, 1% NH_4OEt -10% EtOH-90% CHCl_3) afforded the title compound (28) which was converted to the hydrochloride salt after treatment with methanolic 10 HCl .

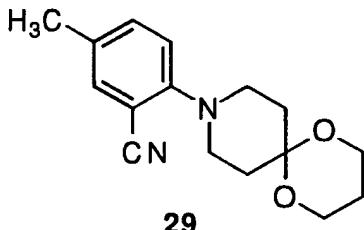
^1H NMR (CDCl_3 , 400 MHz) consistent with assigned structure.

FABLRMS m/e 651 g/mole (M^++H , $\text{C}_{30}\text{H}_{31}\text{F}_5\text{N}_6\text{O}_5 = 651$ g/mole.)

15 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H_2O [0.1% H_3PO_4] - CH_3CN , 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) RT = 10.49 min; focus = 215 nm; 97.7% pure.

Anal. Calcd for $\text{C}_{30}\text{H}_{31}\text{F}_5\text{N}_6\text{O}_5 \bullet 1.15 \text{ HCl}$: C = 52.03, H = 20 4.68, N = 12.14. Found: C = 52.17, H = 4.45, N = 11.76.

EXAMPLE 27

*N*-(2-Cyano-4-methylphenyl)-4-piperidone propylene ketal (29)

A solution of 2-fluoro-5-methylbenzonitrile (2.76 g, 20.4 mmol) and 4-piperidone propylene ketal (3.39 g, 21.5 mmol) in DMF (50 mL) was heated in an oil bath (90 °C, 20 h). The mixture was diluted with ether and sodium carbonate solution. The aqueous layer was extracted with two additional portions of ether and the combined organic extracts were washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. PCTLC (SiO₂, 6mm, 50 - 0% hexane/ CHCl₃) afforded the title compound (29).

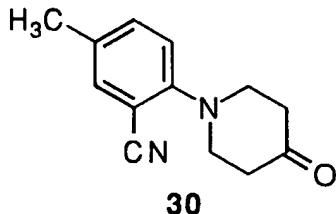
15 ¹H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

FABLRMS m/e 273 g/mole (M⁺+H, C₁₆H₂₀N₂O₂ = 273 g/mole.)

15 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) RT = 9.97 min; focus = 215 nm; 97.8% pure.

20

EXAMPLE 28

*N*-(2-Cyano-4-methylphenyl)-4-piperidone (30)

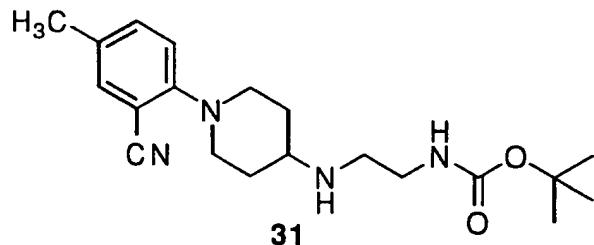
A solution of 29 (549 mg, 2.00 mmol) in ether (20 mL) was treated with 3N aqueous HCl (25 mL). The mixture was stirred at room temperature (24 h). The solvent was removed in vacuo and the residue dissolved in 6N HCl (25 mL) and acetic acid (10 mL). The mixture was stirred at room temperature (3 h). The reaction mixture was neutralized with sodium carbonate solution and the aqueous layer was extracted with three portions of ether. The combined organic extracts were washed with brine, dried over Na_2SO_4 , and concentrated under reduced pressure to afford the title compound (30).

10 FABLRMS m/e 215 g/mole (M^++H , $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O} = 215$ g/mole.)

15 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H_2O [0.1% H_3PO_4] - CH_3CN , 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) RT = 8.55 min; focus = 215 nm; 88.5% pure.

15

EXAMPLE 29



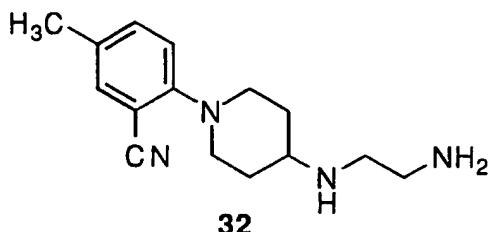
(2-(1-(2-Cyano-4-methylphenyl)piperidin-4-ylamino)ethyl)carbamic acid *tert*-butyl ester (31)

20 Following the procedure of Example 7, but using (30) in place of (8), the crude product was obtained. PCTLC (SiO_2 , 4mm, 10% EtOH-90% CHCl_3) afforded the title compound (31).

25 FABLRMS m/e 359 g/mole (M^++H , $\text{C}_{20}\text{H}_{30}\text{N}_4\text{O}_2 = 359$ g/mole.)

HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H_2O [0.1% H_3PO_4] - CH_3CN , 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) RT = 8.36 min; focus = 215 nm; 100% pure.

EXAMPLE 30

2-(4-(2-Aminoethylamino)piperidin-1-yl)-5-methylbenzonitrile (32)

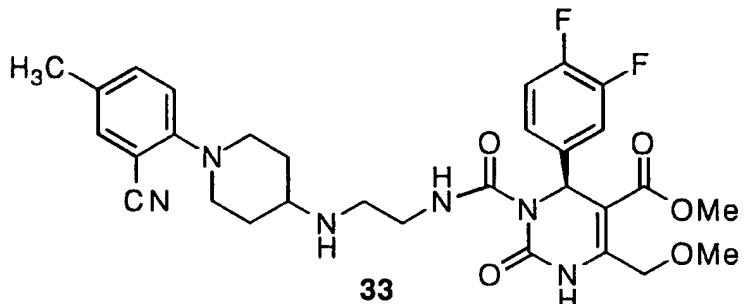
Following the procedure of Example 14, but using (31) in
5 place of (15), the title compound (32) was obtained.

FABLRMS m/e 259 g/mole (M^++H , $C_{15}H_{22}N_4 = 259$ g/mole.)

HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm;
gradient = H_2O [0.1% H_3PO_4] - CH_3CN , 95% - 5%, 5% - 95%, over 16
minutes, 2 ml/min flow rate) RT = 5.98 min; focus = 215 nm; 100% pure.

10

EXAMPLE 31



15 (4S)-3-(2-(1-(2-Cyano-4-methylphenyl)piperidin-4-amino)ethylcarbamoyl)-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester (33)

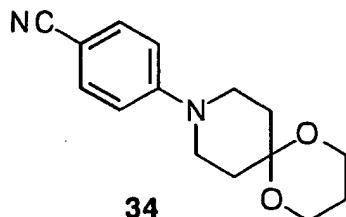
Following the procedure of Example 15, but using (32) in
place of (16), the crude product was obtained. PCTLC (SiO_2 , 2mm, 10%
 $EtOH$; 90% $CHCl_3$) afforded the title compound (33) as the hydrochloride
salt after treatment with $EtOAc/HCl$.

20 1H NMR ($CDCl_3$, 400 MHz) consistent with assigned
structure.

FABLRMS m/e 597 g/mole (M^++H , $C_{30}H_{34}F_2N_6O_5 = 597$ g/mole.)

HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H_2O [0.1% H_3PO_4] - CH_3CN , 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) RT = 9.79 min; focus = 215 nm; 99.7% pure.

EXAMPLE 32



N-(4-Cyanophenyl)-4-piperidone propylene ketal (34)

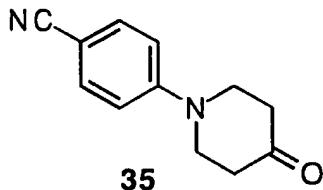
10 A mixture of 4-fluorobenzonitrile (1.22 g, 10.0 mmol) and 4-piperidone propylene ketal (2.02 g, 12.85 mmol) was stirred at room temperature overnight. The resulting mixture was diluted with dichloromethane and sodium carbonate solution and the aqueous layer was extracted with two additional portions of dichloromethane. The 15 combined organic extracts were washed with brine and dried over Na_2SO_4 . The solvent was removed in vacuo. PCTLC (SiO_2 , 6mm, 10% EtOH-90% $CHCl_3$) afforded the title compound (34).

1 1H NMR ($CDCl_3$, 400 MHz) consistent with assigned structure.

20 FABLRMS m/e 259 g/mole (M^++H , $C_{15}H_{18}N_2O_2 = 259$ g/mole.)

HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H_2O [0.1% H_3PO_4] - CH_3CN , 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) RT = 8.62 min; focus = 215 nm; 100% pure.

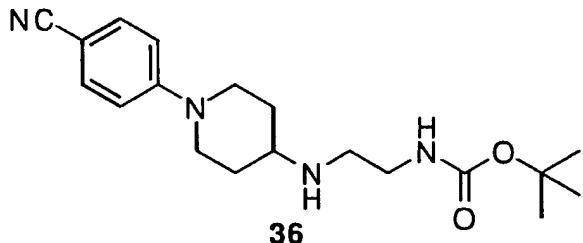
EXAMPLE 33

*N*-(4-Cyanophenyl)-4-piperidone (35)

5 A solution of 34 (915 mg, 3.54 mmol) in ether (6 mL) was treated with 6N aqueous HCl (25 mL). The mixture was stirred at room temperature (2 d). The solvent was removed in vacuo and the residue dissolved in 3N HCl (25 mL) and acetic acid (20 mL). The mixture was stirred at room temperature (2 h). The solvent was removed in vacuo and the residue dissolved in dichloromethane and sodium carbonate solution. The aqueous layer was extracted with two additional portions of dichloromethane and the combined organic extracts were washed with brine, dried over Na_2SO_4 , and concentrated under reduced pressure. PCTLC (SiO_2 , 4mm, 10% EtOH-90% CHCl_3) afforded the title compound (35).

15 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H_2O [0.1% H_3PO_4] - CH_3CN , 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) RT = 6.86 min; focus = 215 nm; 99% pure.

EXAMPLE 34



20

(2-(1-(4-Cyanophenyl)piperidin-4-ylamino)ethyl)carbamic acid *tert*-butyl ester (36)

A solution of 35 (415 mg, 2.07 mmol), 1 (343 mg, 2.14 mmol), and acetic acid (629 mg, 10.48 mmol) in methanol (10 mL) was treated

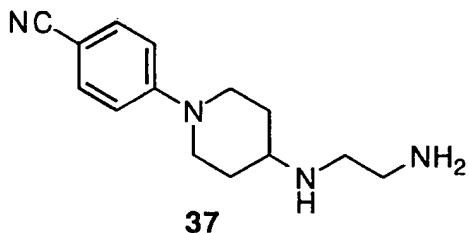
with sodium cyanoborohydride (140 mg, 2.23 mmol) at room temperature. The resulting mixture was stirred at room temperature (3 h). The solvent was removed in vacuo. PCTLC (SiO₂, 4mm, 10% EtOH-90% CHCl₃) afforded the title compound (36).

5 ¹H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

FABLRMS m/e 345 g/mole (M⁺+H, C₁₉H₂₈N₄O₂ = 345 g/mole.)

10

EXAMPLE 35

4-(4-(2-Aminoethylamino)piperidin-1-yl)benzonitrile (37)

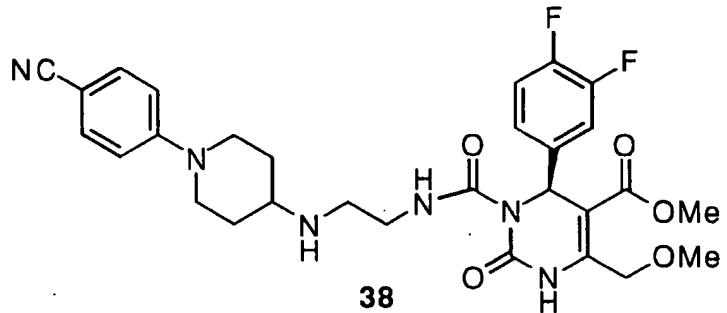
Following the procedure of Example 14, but using (36) in place of (15), the title compound (37) was obtained.

15 FABLRMS m/e 245 g/mole (M⁺+H, C₁₄H₂₀N₄ = 245 g/mole.)

HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) RT = 4.91 min; focus = 215 nm; 94.3% pure.

20

EXAMPLE 36



(4S)-3-(2-(1-(4-Cyanophenyl)piperidin-4-ylamino)ethylcarbamoyl)-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester (38)

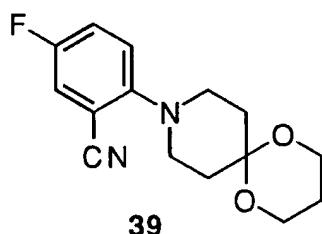
5 Following the procedure of Example 12, but using (37) in place of (13), the crude product was obtained. PCTLC (SiO₂, 2mm, 10% EtOH-90% CHCl₃) afforded the title compound (38) as the hydrochloride salt after treatment with EtOAc/HCl.

10 ¹H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

10 FABLRMS m/e 583 g/mole (M⁺⁺H, C₂₉H₃₂F₂N₆O₅ = 583 g/mole.)

15 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) RT = 9.11 min; focus = 215 nm; 96.9% pure. Anal. Calcd for C₂₉H₃₂F₂N₆O₅ • 0.95 HCl • 0.60 water: C = 55.45, H = 5.48, N = 13.38 Found: C = 55.49, H = 5.47, N = 13.03.

EXAMPLE 37



20 **N-(2-Cyano-4-fluorophenyl)-4-piperidone propylene ketal (39)**

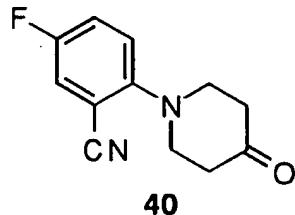
20 A mixture of 2,5-difluorobenzonitrile (2.272 g, 16.33 mmol) and 4-piperidone propylene ketal (2.570 g, 16.34 mmol) was stirred at room temperature (11 d). The resulting mixture was diluted with dichloromethane and sodium carbonate solution and the aqueous layer was extracted with two additional portions of dichloromethane. The combined organic extracts were washed with brine and dried over Na₂SO₄. The solvent was removed in vacuo. PCTLC (SiO₂, 6mm, 20% EtOAc-80% hexane) afforded the title compound (39).

¹H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

FABLRMS m/e 277 g/mole (M⁺+H, C₁₅H₁₇FN₂O₂ = 277 g/mole.)

5 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) RT = 7.31 min; focus = 215 nm; 99.3% pure.

EXAMPLE 38



10

N-(2-Cyano-4-fluorophenyl)-4-piperidone (40)

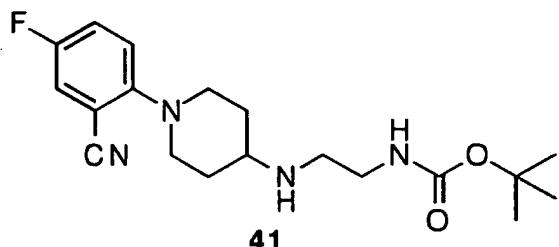
A solution of 39 (1.483 g, 5.36 mmol) in 6N aqueous HCl (25 mL) was treated with acetic acid (50 mL) at room temperature. The mixture was stirred at room temperature (3 d). The solvent was 15 removed in vacuo and the residue dissolved in dichloromethane and sodium carbonate solution. The aqueous layer was extracted with three additional portions of dichloromethane and the combined organic extracts were washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. PCTLC (SiO₂, 6mm, 20% EtOAc-80% hexane) 20 afforded the title compound (40).

¹H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

FABLRMS m/e 219 g/mole (M⁺+H, C₁₂H₁₁FN₂O = 219 g/mole.)

25 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) RT = 7.95 min; focus = 215 nm; 98.2% pure.

EXAMPLE 39



(2-(1-(2-Cyano-4-fluorophenyl)piperidin-4-ylamino)ethyl)carbamic acid
tert-butyl ester (41)

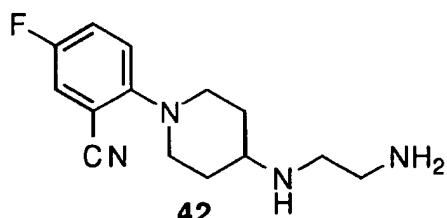
5 Following the procedure of Example 19, but using (40) in place of (20), the crude product was obtained. PCTLC (SiO_2 , 4mm, 1% NH_4OEt -10% EtOH-90% CHCl_3) afforded the title compound (41).

FABLRMS m/e 363 g/mole (M^++H , $\text{C}_{19}\text{H}_{27}\text{FN}_4\text{O}_2$ = 363

g/mole.)

10 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H_2O [0.1% H_3PO_4] - CH_3CN , 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) RT = 8.37 min; focus = 215 nm; 99% pure.

EXAMPLE 40



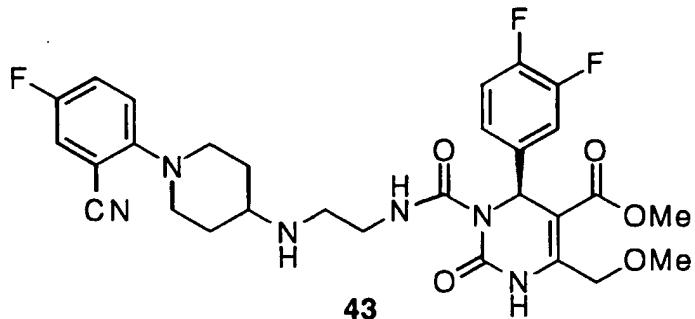
15

2-(4-(2-Aminoethylamino)piperidin-1-yl)-5-fluorobenzonitrile (42)

Following the procedure of Example 14, but using (41) in place of (14), the title compound (42) was obtained.

20 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H_2O [0.1% H_3PO_4] - CH_3CN , 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) RT = 5.84 min; focus = 215 nm; 100% pure.

EXAMPLE 41



(4S)-3-(2-(1-(2-Cyano-4-fluorophenyl)-piperidin-4-ylamino)ethylcarbamoyl)-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-1,2,3,4-

5 tetrahydropyrimidine-5-carboxylic acid methyl ester (43)

Following the procedure of Example 12, but using (42) in place of (13), the crude product was obtained. PCTLC (SiO_2 , 2mm, 1% NH_4OEt -10% EtOH-90% CHCl_3) afforded the title compound (43) which was converted to the hydrochloride salt after treatment with EtOAc/HCl .

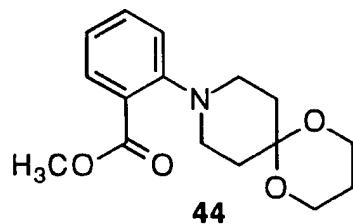
10 ^1H NMR (CDCl_3 , 400 MHz) consistent with assigned structure.

FABLRMS m/e 601 g/mole (M^++H , $\text{C}_{29}\text{H}_{31}\text{F}_3\text{N}_6\text{O}_5 = 601$ g/mole.)

15 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H_2O [0.1% H_3PO_4] - CH_3CN , 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) RT = 9.75 min; focus = 215 nm; 100% pure. Anal. Calcd for $\text{C}_{29}\text{H}_{31}\text{F}_3\text{N}_6\text{O}_5 \bullet 1.10 \text{ HCl}$: C = 54.36, H = 5.05, N = 13.12 Found: C = 54.28, H = 5.20, N = 13.34.

20

EXAMPLE 42



N-(2-Carbomethoxyphenyl)-4-piperidone propylene ketal (44)

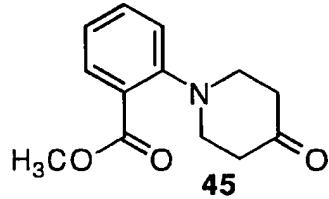
A mixture of methyl 2-fluorobenzoate (16.0 g, 103.8 mmol) and 4-piperidone propylene ketal (9.8 g, 62.3 mmol) was stirred at room temperature (8 d). Flash chromatography on silica gel (10% MeOH-90% CHCl₃) afforded the title compound (44).

5 ¹H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

FABLRMS m/e 292 g/mole (M⁺+H, C₁₆H₂₁NO₄ = 292 g/mole.)

10 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) RT = 4.96 min; focus = 215 nm; 93.2% pure.

EXAMPLE 43

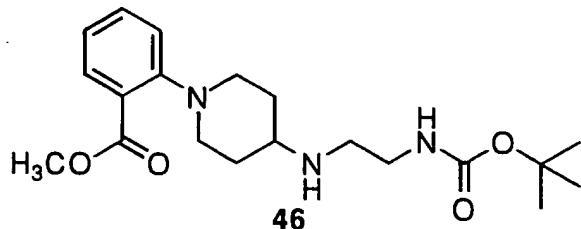
N-(2-Carbomethoxyphenyl)-4-piperidone (45)

A mixture of 44 (5.3 g, 18 mmol) in methanolic HCl (200 mL) was heated in an oil bath (50 °C, 1h). The resulting mixture was cooled, diluted with water (50 mL), and stirred at room temperature (30 min).

20 The solvent volume was reduced in vacuo and neutralized with sodium carbonate. The aqueous layer was extracted with three portions of dichloromethane. The combined organic extracts were washed with brine and dried over Na₂SO₄. The solvent was removed in vacuo. PCTLC (SiO₂, 6mm, 10% EtOH-90% CHCl₃) afforded the title compound (45).

25 ¹H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

EXAMPLE 44



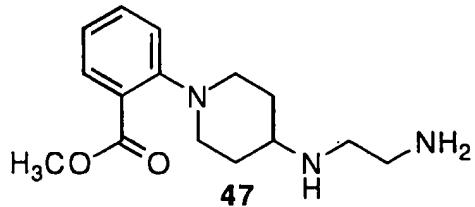
2-(4-(2-*tert*-Butoxycarbonylaminoethylamino)piperidin-1-yl)benzoic acid methyl ester (46)

5 A solution of 45 (195 mg, 0.836 mmol), 1 (175 mg, 1.09 mmol), and acetic acid (251 mg, 4.19 mmol) in methanol (3 mL)/ dichloroethane (1 mL) was treated with sodium cyanoborohydride (55 mg, 0.875 mmol) at room temperature. The resulting mixture was stirred at room temperature (3 h). The solvent was removed in vacuo
 10 and the residue dissolved in dichloromethane and sodium carbonate solution. The aqueous layer was extracted with two additional portions of dichloromethane and the combined organic extracts were washed with brine, dried over Na_2SO_4 , and concentrated under reduced pressure. PCTLC (SiO_2 , 4mm, 1% NH_4OEt -10% EtOH-90% CHCl_3)
 15 afforded the title compound (46).

^1H NMR (CDCl_3 , 400 MHz) consistent with assigned structure.

20 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H_2O [0.1% H_3PO_4] - CH_3CN , 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) RT = 6.61 min; focus = 215 nm; 94.2% pure.

EXAMPLE 45

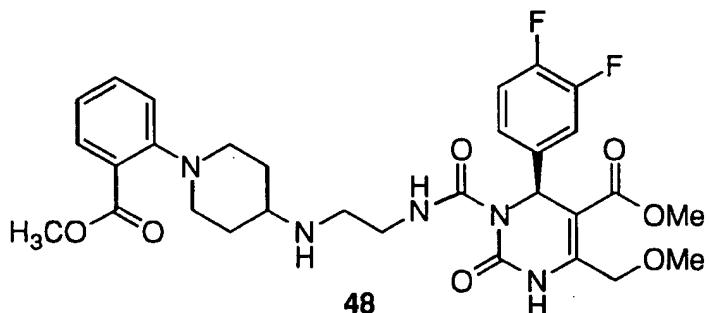


2-(4-(2-Aminoethylamino)piperidin-1-yl)benzoic acid methyl ester (47)

Following the procedure of Example 14, but using (46) in place of (15), the title compound (47) was obtained.

HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) RT = 4.64 min; focus = 215 nm; 92.4% pure.

EXAMPLE 46



(4S)-4-(3,4-Difluorophenyl)-3-(2-(1-(2-methoxycarbonylphenyl)piperidin-4-ylamino)ethylcarbamoyl)-6-methoxymethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester (48)

A solution of 2 (75 mg, 0.157 mmol) in dichloromethane (1 mL) was treated with a solution of 47 (43 mg, 0.155 mmol) in dichloromethane (1 mL) at room temperature. The mixture was stirred at room temperature overnight. The mixture was diluted with sodium carbonate solution and the aqueous layer was extracted with two additional portions of dichloromethane. The combined organic extracts were washed with brine and dried over Na₂SO₄. The solvent was removed in vacuo. PCTLC (SiO₂, 2mm, 1% NH₄OEt-10% EtOH-90% CHCl₃) afforded the title compound (48) which was converted to the hydrochloride salt after treatment with EtOAc/HCl.

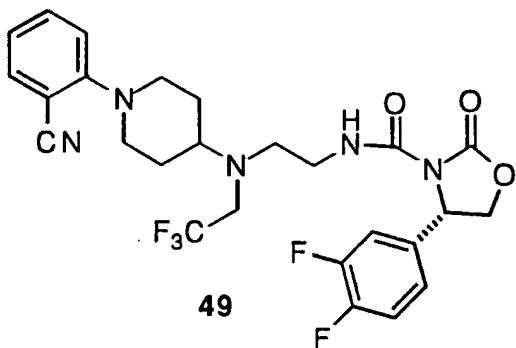
¹H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

FABLRMS m/e 616 g/mole (M⁺+H, C₃₀H₃₅F₂N₅O₇ = 616 g/mole.)

HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) RT = 8.66 min; focus = 215 nm; 97.1% pure.

5

EXAMPLE 47



(4S)-4-(3,4-Difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid (2-((1-(2-cyanophenyl)piperidin-4-yl)-(2,2,2-trifluoroethyl)amino)ethyl)amide (49)

A solution of 18 (36 mg, 0.076 mmol) and cesium carbonate 10 (50 mg, 0.153 mmol) in acetonitrile (100 mL) was treated with 2,2,2-trifluoroethyl iodide (21.3 mg, 0.101 mmol) at room temperature. The resulting mixture was stirred at room temperature overnight. The mixture was diluted with dichloromethane and water and the aqueous layer was extracted with two additional portions of dichloromethane.

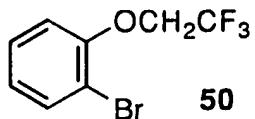
15 The combined organic extracts were concentrated under reduced pressure and purified by PCTLC (SiO₂, 4mm, 1% NH₄OEt-1% NH₄OEt-10% EtOH-90% CHCl₃) to afford the title compound (49) which was converted to the hydrochloride salt after treatment with EtOAc/HCl.

20 ¹H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

FABLRMS m/e 553 g/mole (M⁺+H, C₂₆H₂₆F₅N₅O₃ = 553 g/mole.)

25 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) RT = 7.95 min; focus = 215 nm; 92.3% pure.

EXAMPLE 48

1-Bromo-2-(2,2,2-trifluoroethoxy)benzene (50)

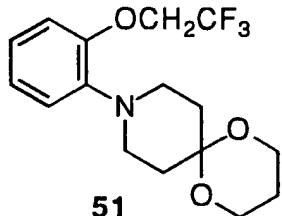
5 A solution of 2-bromophenol (5.89 g, 34.0 mmol) and 2,2,2-trifluoroethyliodide (16.8 g, 80.0 mmol) in DMF (60 mL) was treated with potassium carbonate (24.1 g, 174 mmol) at room temperature. The resulting mixture was heated in an oil bath (60 °C, 2 d). The solvent was removed in vacuo and the residue dissolved in ether and water. The 10 aqueous layer was extracted with two additional portions of ether and the combined organic extracts were washed with three portions of 1M NaOH solution and dried over Na₂SO₄. The solvent was removed in vacuo to afford the title compound (50).

15 ¹H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) RT = 11.42 min; focus = 215 nm; 93.2% pure.

20

EXAMPLE 49

N-(2-(2,2,2-Trifluoroethoxy)phenyl)-4-piperidone propylene ketal (51)

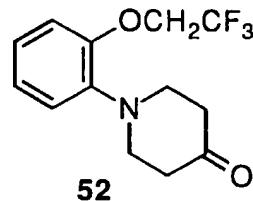
25 A solution of 50 (1.786 g, 7.00 mmol) and 4-piperidone propylene ketal (2.645 g, 16.82 mmol) in toluene (30 mL) was treated with sodium tert-butoxide (1.88 g, 19.56 mmol), (S)-BINAP (44 mg, 0.07

mmol), and tris(dibenzylideneacetone)dipalladium(0) (32 mg, 0.035 mmol) at room temperature. The mixture was heated in an oil bath (80 °C, 3 h). The mixture was diluted with ether and brine. The aqueous layer was extracted with two additional portions of ether and the 5 combined organic extracts were washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. PCTLC (SiO₂, 6mm, 20% EtOAc-80% hexane) afforded the title compound (51).

10 ¹H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

11 FABLRMS m/e 332 g/mole (M⁺⁺H, C₁₆H₂₀F₃NO₃ = 332 g/mole.)

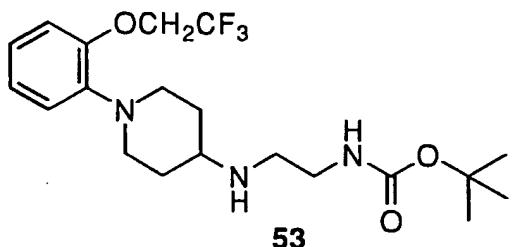
EXAMPLE 50



15 N-(o-(2,2,2-Trifluoroethoxy)phenyl)-4-piperidone (52)
 A solution of 51 (410 mg, 1.23 mmol) in acetic acid (20 mL), water (20 mL), and concentrated HCl (5 mL) was heated in an oil bath (60 °C) overnight. The solvent was removed in vacuo and the residue dissolved in dichloromethane and sodium bicarbonate solution. The 20 aqueous layer was extracted with two additional portions of dichloromethane and the combined organic extracts were washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. PCTLC (SiO₂, 4mm, 10% EtOH-90% CHCl₃) afforded the title compound (52)

25 ¹H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

EXAMPLE 51



(2-(1-(2,2,2-Trifluoroethoxy)phenyl)piperidin-4-ylamino)ethylcarbamic acid *tert*-butyl ester (53)

5 Following the procedure of Example 19, but using (52) in place of (20), the crude product was obtained. PCTLC (SiO_2 , 4mm, 1% NH_4OEt -10% EtOH-90% CHCl_3) afforded the title compound (53).

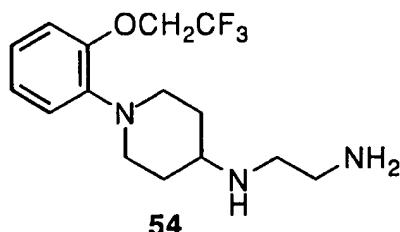
10 ^1H NMR (CDCl_3 , 400 MHz) consistent with assigned structure.

15 FABLRMS m/e 418 g/mole (M^++H , $\text{C}_{20}\text{H}_{30}\text{F}_3\text{N}_3\text{O}_3 = 418$ g/mole.)

HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H_2O [0.1% H_3PO_4] - CH_3CN , 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) RT = 8.04 min; focus = 215 nm; 97.4% pure.

15

EXAMPLE 52



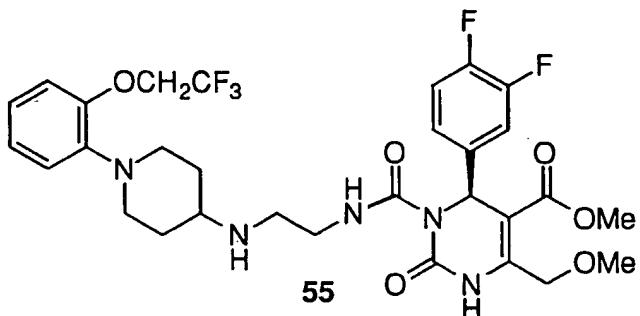
N_1 -(1-(2,2,2-Trifluoroethoxy)phenyl)piperidin-4-yl)ethane-1,2-diamine (54)

20 Following the procedure of Example 14, but using (53) in place of (15), the title compound (54) was obtained.

HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) RT = 5.84 min; focus = 215 nm; 100% pure.

5

EXAMPLE 53



(4S)-4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(1-(2-(2,2,2-trifluoroethoxy)phenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester (55)

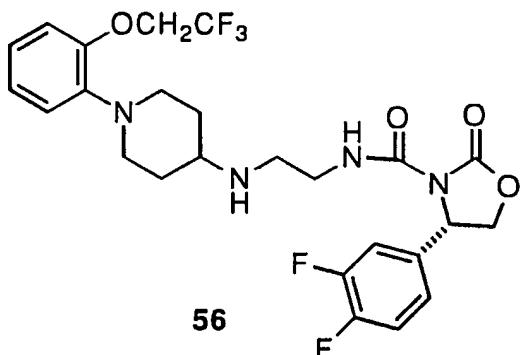
10 A solution of 54 (74 mg, 0.233 mmol) in dichloromethane (1 mL) was treated with 2 (122 mg, 0.255 mmol) at room temperature. The mixture was stirred at room temperature (5 min). The mixture was diluted with sodium carbonate solution and the aqueous layer was extracted with two additional portions of dichloromethane. The 15 combined organic extracts were washed with brine and dried over Na₂SO₄. The solvent was removed in vacuo. PCTLC (SiO₂, 2mm, 1% NH₄OEt-10% EtOH-90% CHCl₃) afforded the title compound (55) as the hydrochloride salt after treatment with EtOAc/HCl.

20 ¹H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

25 FABLRMS m/e 656 g/mole (M⁺⁺H, C₃₀H₃₄F₅N₅O₆ = 656 g/mole.)

HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) RT = 9.86 min; focus = 215 nm; 100% pure.

EXAMPLE 54



(4S)-4-(3,4-Difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid (2-(1-(2-(2,2,2-trifluoroethoxy)phenyl)piperidin-4-ylamino)ethyl)amide (56)

5 A solution of 54 (94 mg, 0.296 mmol) in dichloromethane (1 mL) was treated with 3 (109 mg, 0.299 mmol) at room temperature. The mixture was stirred at room temperature (20 min). The mixture was diluted with sodium carbonate solution and the aqueous layer was extracted with two additional portions of dichloromethane. The

10 combined organic extracts were washed with brine and dried over Na_2SO_4 . The solvent was removed in vacuo. PCTLC (SiO_2 , 2mm, 1% NH_4OEt -10% EtOH-90% CHCl_3) afforded the title compound (56) which was converted to the hydrochloride salt after treatment with EtOAc/HCl .

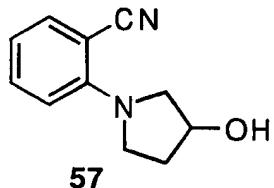
15 ^1H NMR (CDCl_3 , 400 MHz) consistent with assigned structure.

 FABLRMS m/e 543 g/mole (M^++H , $\text{C}_{25}\text{H}_{27}\text{F}_5\text{N}_4\text{O}_4 = 543$ g/mole.)

 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H_2O [0.1% H_3PO_4] - CH_3CN , 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) RT = 8.81 min; focus = 215 nm; 99.2% pure.

20 Anal. Calcd for $\text{C}_{25}\text{H}_{27}\text{F}_5\text{N}_4\text{O}_4 \bullet 0.75 \text{ HCl} \bullet 1.80$ water: C = 49.85, H = 5.25, N = 9.30 Found: C = 49.85, H = 5.25, N = 8.91.

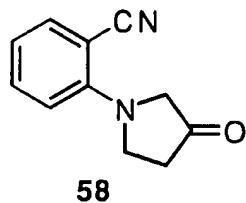
EXAMPLE 55

*N*-(2-Cyanophenyl)-pyrrolidin-2-ol (57)

A mixture of 2-fluorobenzonitrile (4.03 g, 33.2 mmol) and 5 pyrrolidin-2-ol (2.92 g, 33.5 mmol) was treated with diisopropylethylamine (4.37 g, 33.8 mmol) at room temperature. The mixture was stirred at room temperature (5 d). The resulting mixture was diluted with dichloromethane and sodium carbonate solution and the aqueous layer was extracted with two additional portions of dichloromethane. The 10 combined organic extracts were washed with brine and dried over Na_2SO_4 . The solvent was removed in vacuo. PCTLC (SiO_2 , 6mm, 20% EtOAc-80% hexane) afforded the title compound (57).

HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H_2O [0.1% H_3PO_4] - CH_3CN , 95% - 5%, 5% - 95%, over 16 15 minutes, 2 ml/min flow rate) RT = 7.18 min; focus = 215 nm; 98.9% pure.

EXAMPLE 56

*N*-(2-Cyanophenyl)-2-pyrrolidinone (58)

20 A solution of oxalyl chloride (1.58 g, 12.46 mmol) in dichloromethane (50 mL) was treated with DMSO (1.95 g, 24.94 mmol) at -78 °C. The mixture was stirred at -78 °C (10 min) followed by addition of a solution of 57 (2.34 g, 12.43 mmol) in dichloromethane (20 mL) over 10 min. The mixture was stirred at -78 °C (30 min) followed by addition of a 25 triethylamine (4.28 g, 42.33 mmol) over 5 min. The mixture was

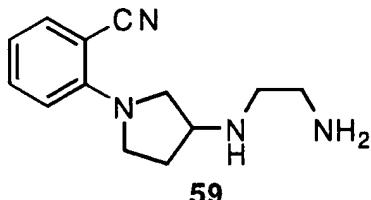
warmed to room temperature and diluted with water (20 mL). The organic extract was washed with brine and dried over Na_2SO_4 . The solvent was removed in vacuo. PCTLC (SiO_2 , 6mm, 10% EtOH-90% CHCl_3) afforded the title compound (58).

5 ^1H NMR (CDCl_3 , 400 MHz) consistent with assigned structure.

HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H_2O [0.1% H_3PO_4] - CH_3CN , 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) RT = 7.70 min; focus = 215 nm; 99.1% pure.

10

EXAMPLE 57



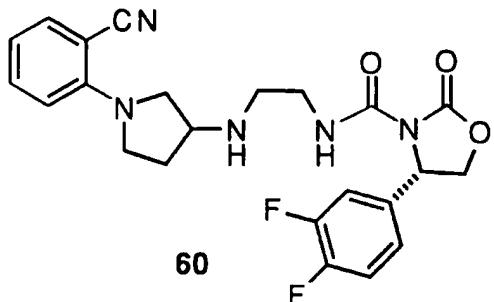
2-(3-(2-Aminoethylamino)pyrrolidin-1-yl)benzonitrile (59)

A solution of 58 (1.33 g, 7.13 mmol), ethylenediamine (4.44 g, 15 73.9 mmol), and p-tolylsulfonic acid (75 mg, 0.394 mmol) in benzene (80 mL) was refluxed (1 h) with removal of water. The solvent was removed in vacuo and the residue dissolved in methanol (40 mL) and treated with sodium cyanoborohydride (480 mg, 7.64 mmol). The mixture was stirred at room temperature overnight. The solvent was removed in vacuo and 20 the residue dissolved in dichloromethane and sodium carbonate solution. The aqueous layer was extracted with two additional portions of dichloromethane and the combined organic extracts were washed with brine, dried over Na_2SO_4 , and concentrated under reduced pressure. PCTLC (SiO_2 , 6mm, 1% NH_4OEt -10% EtOH-90% CHCl_3) afforded the title compound (59)

25 FABLRMS m/e 231 g/mole (M^++H , $\text{C}_{13}\text{H}_{18}\text{N}_4 = 231$ g/mole.)

HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H_2O [0.1% H_3PO_4] - CH_3CN , 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) RT = 5.27 min; focus = 215 nm; 98.7% pure.

EXAMPLE 58



(4S)-4-(3,4-Difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid (2-(1-(2-

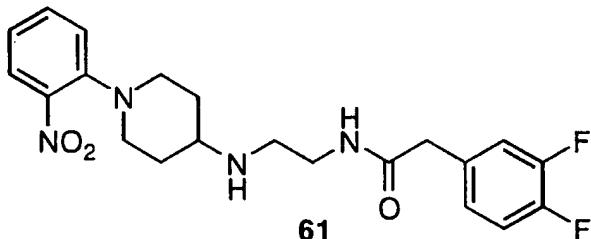
5 cyanophenyl) pyrrolidin-3-ylamino)ethyl)amide (60)

A solution of 59 (115 mg, 0.499 mmol) in dichloromethane (2 mL) was treated with 3 (164 mg, 0.450 mmol) at room temperature. The mixture was stirred at room temperature (1 h). The mixture was diluted with sodium carbonate solution and the aqueous layer was extracted with two additional portions of dichloromethane. The combined organic extracts were washed with brine and dried over Na_2SO_4 . The solvent was removed in vacuo. PCTLC (SiO_2 , 2mm, 1% NH_4OEt -10% EtOH-90% CHCl_3) afforded the title compound (60) which was converted to the hydrochloride salt after treatment with EtOAc/HCl .
 10 ^1H NMR (CDCl_3 , 400 MHz) consistent with assigned structure.
 15

FABLRMS m/e 456 g/mole (M^++H , $\text{C}_{23}\text{H}_{23}\text{F}_2\text{N}_5\text{O}_3 = 456$ g/mole.)

20 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H_2O [0.1% H_3PO_4] - CH_3CN , 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) RT = 8.69 min; focus = 215 nm; 100% pure.
 Anal. Calcd for $\text{C}_{23}\text{H}_{23}\text{F}_2\text{N}_5\text{O}_3 \bullet 0.70 \text{ HCl} \bullet 0.90$ water: C = 55.56, H = 5.17, N = 14.09 Found: C = 55.52, H = 5.16, N = 13.72.

EXAMPLE 59



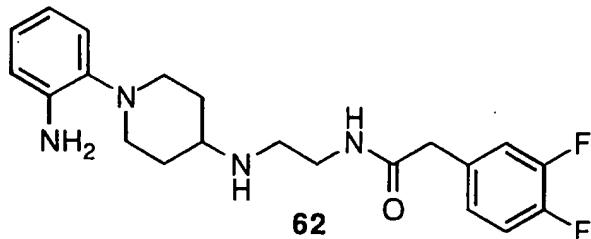
2-(3,4-Difluorophenyl)-N-(2-(1-(2-nitrophenyl)piperidin-4-ylamino)ethyl)acetamide (61)

5 A solution of *N*-(2-nitrophenyl)piperid-4-one (128.7 mg, 0.5844 mmol), *N*-(2-aminoethyl)-1-(3,4-difluorophenyl)acetamide (125.2 mg, 0.5844 mmol), and acetic acid (175 mg, 2.922 mmol) in methanol (2 mL) was treated with sodium cyanoborohydride (37 mg, 0.5844 mmol) at room temperature. The resulting mixture was stirred at room
 10 temperature (50 min). The solvent was removed in vacuo and the residue dissolved in dichloromethane and sodium bicarbonate solution. The aqueous layer was extracted with two additional portions of dichloromethane and the combined organic extracts were washed with brine, dried over Na_2SO_4 , and concentrated under reduced pressure.
 15 PCTLC (SiO_2 , 2 mm, 0 - 5% $\text{MeOH} - \text{CHCl}_3$) afforded the title compound (61).

^1H NMR (CDCl_3 , 400 MHz) consistent with assigned structure.

20 FABLRMS m/e 419.22 g/mole (M^++H , $\text{C}_{21}\text{H}_{24}\text{N}_4\text{O}_3\text{F}_2$ = 419.45 g/mole.)
 Anal. Calcd for $\text{C}_{21}\text{H}_{24}\text{N}_4\text{O}_3\text{F}_2 \bullet 2 \text{ HCl} \& 0.45 \text{ H}_2\text{O}$: C = 50.49, H = 5.43, N = 11.22. Found: C = 50.52, H = 5.37, N = 11.04.
 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H_2O [0.1% H_3PO_4] - CH_3CN , 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) RT = 8.19 min; focus = 215 nm; 98.7% pure.

EXAMPLE 60



N-(2-(1-(2-Aminophenyl)piperidin-4-ylamino)ethyl)-2-(3,4-difluorophenyl)acetamide (62)

5 A solution of nitroaryl (75 mg, 0.1801 mmol) and 10% Pd-C (50 mg) in THF (10 mL) was stirred at room temperature under a hydrogen atmosphere (2 h). The resulting mixture was filtered through Celite, washed with EtOH and concentrated under reduced pressure affording the title compound (62).

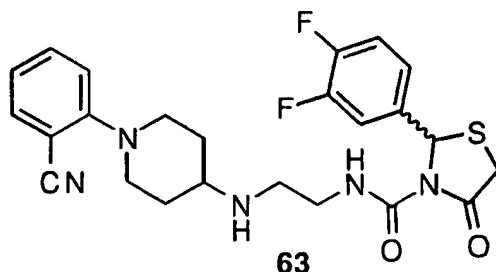
10 ^1H NMR (CDCl_3 , 400 MHz) consistent with assigned structure.

FABLRMS m/e 389.19 g/mole (M^++H , $\text{C}_{21}\text{H}_{26}\text{N}_4\text{OF}_2$ = 389.46 g/mole.)

Anal. Calcd for $\text{C}_{21}\text{H}_{26}\text{N}_4\text{O}_3\text{F}_2 \cdot 3 \text{ HCl}$: C = 50.66, H = 5.87,

15 N = 11.25. Found: C = 50.91, H = 6.15, N = 11.29.

EXAMPLE 61



2-(3,4-Difluorophenyl)-4-oxothiazolidine-3-carboxylic acid (2-(1-(2-cyanophenyl)piperidin-4-ylamino)ethyl)amide (63)

20 A solution of amine (60 mg, 0.2456 mmol) in DMF (1 mL) was treated with a solution of the activated thiazolidinone (0.2456 mmol)

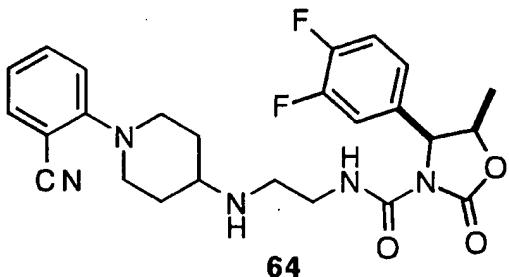
in dichloromethane (1 mL) at room temperature (1 h). The resulting yellow reaction mixture was concentrated in vacuo and submitted to PCTLC (SiO₂, 1 cm, 0 - 10% MeOH-CHCl₃) providing the desired product (63).

5 ¹H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

Anal. Calcd for C₂₄H₂₅N₅O₂SF₂ • 0.4 DMF: C = 58.79, H = 5.44, N = 14.69. Found: C = 58.93, H = 5.07, N = 15.09.

10

EXAMPLE 62



(4S,5R)-4-(3,4-difluorophenyl)-5-methyl-2-oxo-oxazolidine-3-carboxylic acid (2-(1-(2-cyanophenyl)piperidin-4-ylamino)ethyl)amide (64)

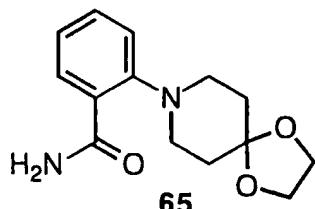
15 A solution of amine (19.4 mg, 0.0793 mmol) in CHCl₃ (1 mL) was treated with a solution of the activated oxazolidinone (0.0793 mmol) in DCM (1 mL) at room temperature. The mixture was stirred at room temperature (1 h). The resulting yellow reaction mixture was concentrated in vacuo and submitted to PCTLC (SiO₂, 1 cm, 0 - 10% MeOH-CHCl₃) providing the desired product (64).

20 ¹H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

Anal. Calcd for C₂₅H₂₇N₅O₃F₂ • 0.4 CHCl₃ : C = 57.42, H = 5.20, N = 13.18. Found: C = 57.27, H = 5.49, N = 13.51.

25 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) RT = 9.10 (cis) and 9.31 (trans) min; focus = 215 nm; 95.5:4.5 pure.

EXAMPLE 63

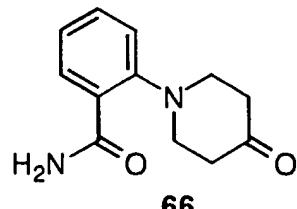
*N*-(2-Benzamido)-4-piperidone ethylene ketal (65)

5 A mixture of 2-fluorobenzamide (7.0 g, 50.0 mmol) and 4-piperidone ethylene ketal (7.16 g, 50.0 mmol) was heated at 100 °C (7 d). The solvent was removed in vacuo and triturated with ether affording the title compound (65).

10 ^1H NMR (DMSO-d₆, 300 MHz) consistent with assigned structure.

15 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 mL/min flow rate) RT = 4.49 min; focus = 215 nm; 100% pure.

EXAMPLE 64



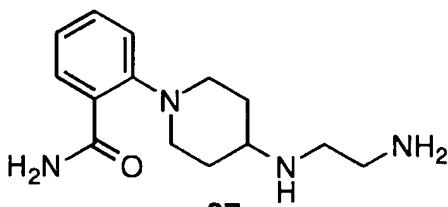
15

N-(2-Benzamido)-4-piperidone (66)

20 A solution of the ketal (13.2 mg, 46.753 mmol) in acetic acid (50 mL) and 6N aqueous HCl (50 mL) was heated at 60 °C (12 h), 80% conversion. The solvent was removed in vacuo, neutralized with 25% aqueous NaOH, extracted with CHCl₃ (3 x 250 mL), the combined organic extracts were washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure to give (66) which was used without further purification.

¹H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

EXAMPLE 65



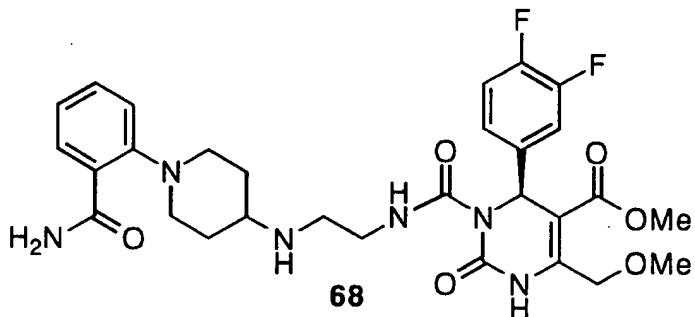
5

2-(4-(2-Aminoethylamino)piperidin-1-yl)benzamide (67)

A solution of the piperidone (2.5 g, 11.4543 mmol), ethylene diamine (6.89 g, 114.543 mmol) and p-toluene sulphonic acid (0.105 g, 0.57272 mmol) in benzene (100 mL) was refluxed under a Dean-Stark trap until cessation of water azeotrope. The solvent was removed in vacuo, diluted with MeOH (50 mL) and treated with NaBH₃CN (0.714 g, 11.4543 mmol) at room temperature (1 h). The solvent was removed in vacuo, diluted with DCM (50 mL) and saturated aqueous sodium bicarbonate (25 mL), partitioned, extracted with DCM (2 x 50 mL), washed with saturated aqueous sodium bicarbonate (2 x 25 mL) and brine (50 mL), dried (Na₂SO₄), filtered and concentrated in vacuo and submitted to PCTLC (SiO₂, 6 mm, 80/20/2 CHCl₃-MeOH-NH₄OH) affording the titled amine (67).

¹H NMR (CDCl₃, 400 MHz) 9.60 (br s, 1 H), 8.16 (dd, 1 H),
 20 7.45 (dd, 1 H), 7.22 (m, 2 H), 5.87 (br s, 1 H), 3.20 (br d, 2 H), 2.70 - 2.90 (m, 6 H), 2.65 (m, 1 H), 2.07 (br d, 2 H), 1.56 (br ddd, 2 H).

EXAMPLE 66



(4*S*)-3-(2-(1-(2-Carbamoylphenyl)piperidin-4-ylamino)ethylcarbamoyl)-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-1,2,3,4-

5 tetrahydropyrimidine-5-carboxylic acid methyl ester (68)

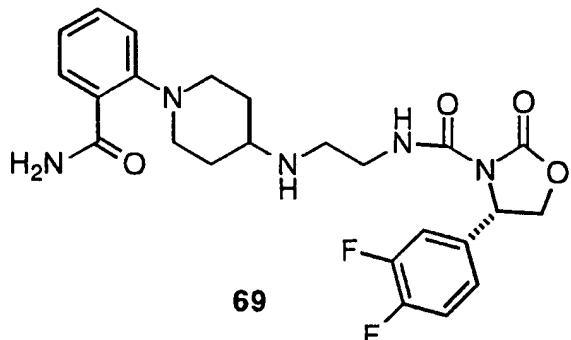
The amine (55 mg, 0.21 mmol) was dissolved in THF and treated with 2 (100 mg, 0.21). The resulting yellow reaction mixture was concentrated in vacuo and submitted to PCTLC (SiO₂, 2 mm, CHCl₃ - 90/10/1 CHCl₃-MeOH-NH₄OH) providing the desired product (68) and a minor less polar material.

10 ¹H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

Anal. Calcd for C₂₉H₃₄N₆O₆F₂ • 0.1 hexane & 1.25 H₂O: C = 56.27, H = 6.05, N = 13.30. Found: C = 56.54, H = 5.65, N = 12.91.

15 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) RT = 7.83 min; focus = 215 nm; 98.8% pure.

EXAMPLE 67



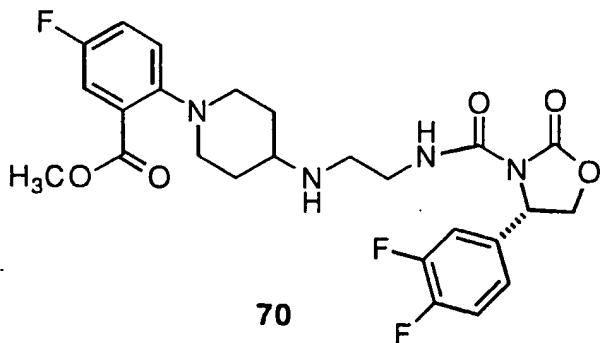
(4S)-4-(3,4-Difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid (2-(1-(2-carbamoylphenyl) piperidin-4-ylamino)ethyl)amide (69)

5 A solution of the amine (72 mg, 0.2745 mmol) in THF (1 mL) was treated with the activated (S)-oxazolidinone (100 mg, 0.2745 mmol) at room temperature. The resulting yellow reaction mixture was concentrated in vacuo and submitted to PCTLC (SiO₂, 2 mm, CHCl₃ - 90/10/1 CHCl₃-MeOH-NH₄OH) providing the desired product (69).

10 ¹H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

15 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) RT = 6.72 min; focus = 215 nm; 99.2% pure. Anal. Calcd for C₂₄H₂₇F₂N₅O₄ • 2.0 HCl • 1.65 water: C = 48.84, H = 5.52, N = 11.87 Found: C = 48.87, H = 5.64, N = 11.99.

EXAMPLE 68



(4S)-4-(3,4-Difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid (2-(1-(4-fluoro-2-methoxycarbonylphenyl)piperidin-4-ylamino)ethyl)amide (70)

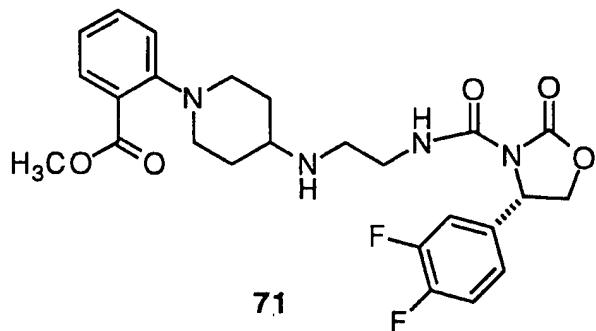
Following the methodology described herein, compound 70 was prepared.

5 ^1H NMR (CDCl_3 , 400 MHz) consistent with assigned structure.

HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H_2O [0.1% H_3PO_4] - CH_3CN , 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) RT = 7.4 min; focus = 215 nm; 99.2% pure.

10 Anal. Calcd for $\text{C}_{25}\text{H}_{27}\text{F}_3\text{N}_4\text{O}_5$ • 2.0 HCl • 0.35 water: C = 50.06, H = 4.99, N = 9.34 Found: C = 50.06, H = 4.96, N = 9.27.

EXAMPLE 69



15 (4S)-4-(3,4-Difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid (2-(1-(2-methoxycarbonylphenyl)piperidin-4-ylamino)ethyl)amide (71)

Following the procedure of Example 16, but using (47) in place of (13), the title compound (71) was obtained.

20 ^1H NMR (CDCl_3 , 400 MHz) consistent with assigned structure.

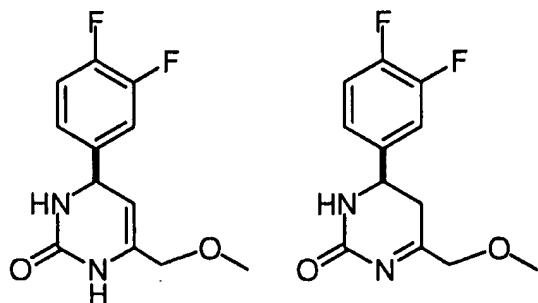
FABLRMS m/e 503 g/mole (M^++H , $\text{C}_{25}\text{H}_{28}\text{F}_2\text{N}_4\text{O}_5$ = 503 g/mole.)

HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H_2O [0.1% H_3PO_4] - CH_3CN , 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) RT = 7.8 min; focus = 215 nm; 99.2% pure.

Anal. Calcd for $C_{25}H_{28}F_2N_4O_5 \cdot 1.95 HCl$: C = 52.34, H = 5.26, N = 9.77 Found: C = 52.33, H = 5.16, N = 9.63.

EXAMPLE 70

5



Mixture of (4S)-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-1,2,3,4-tetrahydropyrimidine and (S-4)-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-1,2,3,4-tetrahydropyrimidine

10

To a solution of (+)-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester (4.63 g, 14.7 mmol) in a methanol (100 ml) was added sodium hydroxide (2.94 g, 73.6 mmol). The resulting mixture was refluxed at 90 °C for 16 hours.

15

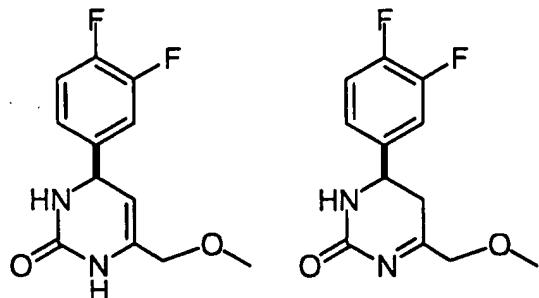
After cooling to room temperature the solvent was removed in vacuo. The solid was dissolved in CH_2Cl_2 and H_2O then neutralized with 10% aqueous HCl solution. The organic layer was dried over Na_2SO_4 , concentrated, and purified by PCTLC (7% MeOH in $CHCl_3$ with 2% NH_4OH) to afford a 2.65 g mixture of the title compounds (71% yield).

20

The 1H NMR was consistent with the assigned structure.

MS (FAB) 255 (M+1)

EXAMPLE 71



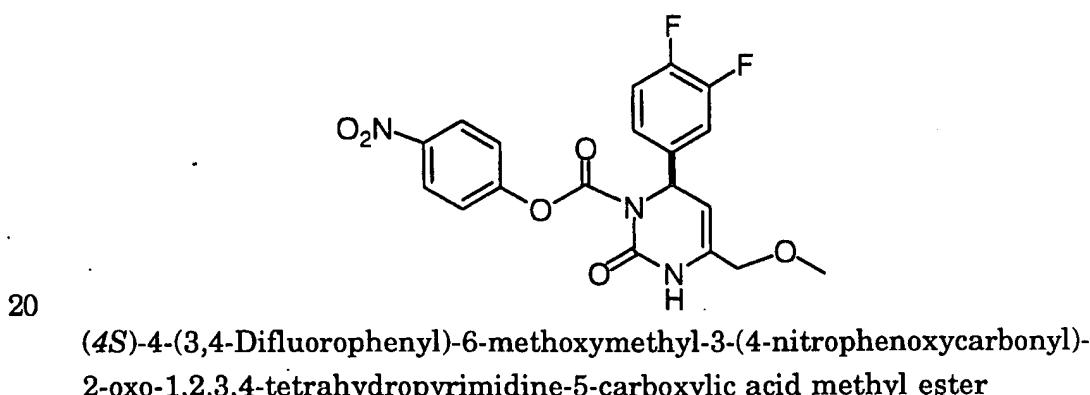
Mixture of *(4S)*-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-1,2,3,4-tetrahydropyrimidine and *(4S)*-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-2,3,4,5-tetrahydropyrimidine

5

To a solution of (+)-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester (5.36 g, 17.0 mmol) in a methanol (150 ml) was added 1N NaOH (10 ml). The resulting mixture was refluxed at 90 °C for 16 hours. After cooling to room temperature the solvent was removed in vacuo. The solid was dissolved in CH₂Cl₂ and H₂O then neutralized with 10% aqueous HCl solution. The organic layer was dried over Na₂SO₄, concentrated, and purified by PCTLC (7% MeOH in CHCl₃ with 2% NH₄OH) to afford a 2.35 g mixture of the title compounds (54% yield). The ¹H NMR was consistent with the assigned structure.

MS (FAB) 255 (M+1)

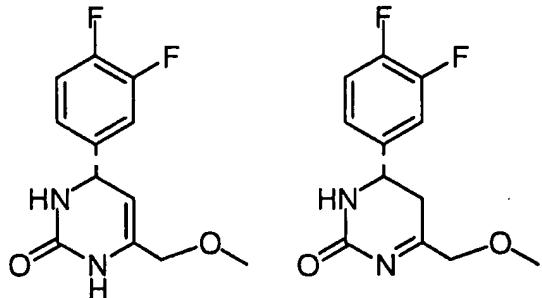
EXAMPLE 72



The title compound was prepared by treating the mixture obtained from Example 70 or Example 71 (1.93 g, 7.59 mmol) with lithium diisopropylamide (2.0M THF solution, 1.1 equivalents) in THF at -78 °C for 20 minutes followed by the rapid addition of 4-nitrophenyl chloroformate (1.5 equivalents) in THF. 0.488 g of the title compound was obtained in a 15% yield. The ¹H NMR was consistent with the assigned structure.

EXAMPLE 73

10



Mixture of (4R)-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-1,2,3,4-tetrahydropyrimidine and (4R)-4-(3,4-difluorophenyl)-6-methoxymethyl-
15 2-oxo-2,3,4,5-tetrahydropyrimidine

The title compounds were prepared from (4R)-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester (5.0 g, 17.7 mmol) using the procedure described in Example 70. A mixture of 2.0 g of the title compounds was obtained in 50% yield. The ¹H NMR was consistent with the assigned structure.

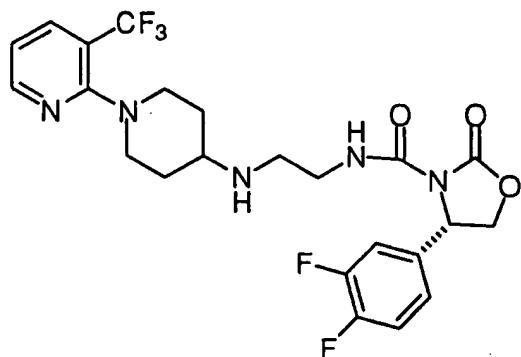
MS (FAB) 255 (M+1)

25 Compounds of the invention can be prepared by reacting the product obtained in Example 72 with a 1-aryl-4-(2-aminoethylamino)piperidine (e.g., compound 42 of Example 40) in accordance with Scheme 2. Compounds of the invention can also be prepared by preparing the nitrophenoxy derivative of the compound of

Example 73 in accordance with the procedure set forth in Example 72 and then reacting the derivative with a 1-aryl-4-(2-aminoethylamino)piperidine in accordance with Scheme 2.

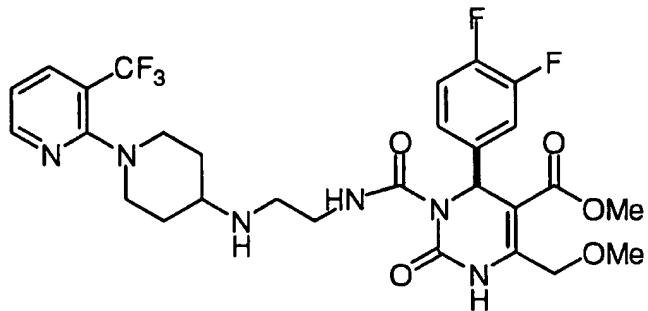
5 The following compounds were prepared in accordance with procedures set forth in the preceding Examples and Schemes.

EXAMPLE 74



10 (4S)-4-(3,4-Difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid (2-(2-(3-trifluoromethylpyridyl)piperidin-4-ylamino)ethyl)amide
¹H NMR (CDCl₃, 400 MHz) consistent with assigned structure.
 FABLRMS m/e 514 g/mole (M⁺+H, C₂₃H₂₄F₅N₅O₃ = 513
 15 g/mole.)
 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 mL/min flow rate) focus = 215 nm; >95% pure.
 Anal. Calcd for C₂₃H₂₄F₅N₅O₃ • 1.55 TFA • 0.40 H₂O: C =
 20 44.89, H = 3.82, N = 10.03. Found: C = 44.90, H = 3.79, N = 10.01.

EXAMPLE 75



5 (4S)-4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-(3-trifluoromethylpyridyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester

10 ^1H NMR (CDCl_3 , 400 MHz) consistent with assigned structure.

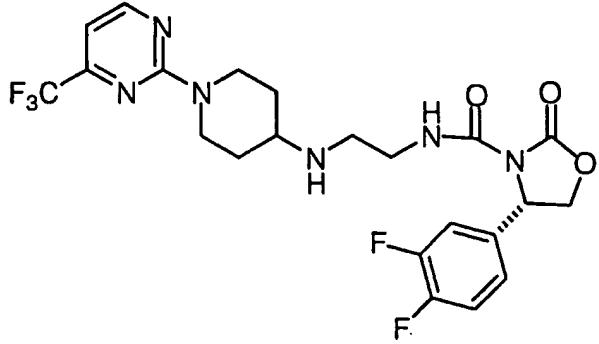
FABLRMS m/e 627 g/mole (M^++H , $\text{C}_{28}\text{H}_{31}\text{F}_5\text{N}_6\text{O}_5 = 626$ g/mole.)

15 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H_2O [0.1% H_3PO_4] - CH_3CN , 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) focus = 215 nm; >95% pure.

Anal. Calcd for $\text{C}_{28}\text{H}_{31}\text{F}_5\text{N}_6\text{O}_5 \bullet 1.55 \text{ TFA} \bullet 0.30 \text{ H}_2\text{O}$: C = 46.19, H = 4.13, N = 10.39. Found: C = 46.18, H = 4.05, N = 10.50.

15

EXAMPLE 76



(4S)-4-(3,4-Difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid (2-(2-(4-trifluoromethylpyrimidyl)piperidin-4-ylamino)ethyl)amide

¹H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

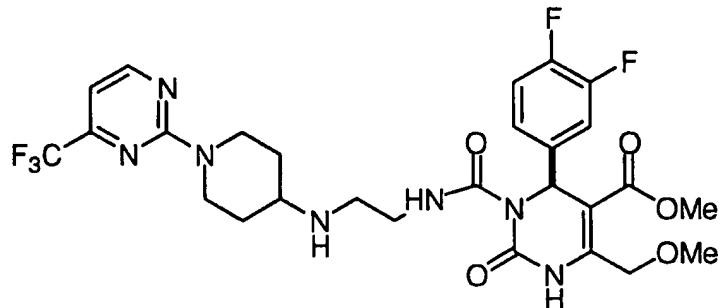
FABLRMS m/e 515 g/mole (M⁺+H, C₂₂H₂₃F₅N₆O₃ = 514 g/mole.)

5 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) focus = 215 nm; >98% pure.

Anal. Calcd for C₂₂H₂₃F₅N₆O₃: C = 51.36, H = 4.51, N = 16.34. Found: C = 51.37, H = 4.45, N = 16.29.

10

EXAMPLE 77



(4S)-4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(4-trifluoromethylpyrimidinyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester

15 1H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

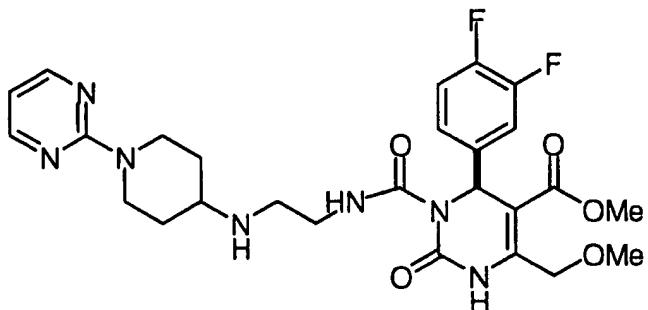
FABLRMS m/e 628 g/mole (M⁺+H, C₂₇H₂₉F₅N₆O₅ = 627 g/mole.)

20 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) focus = 215 nm; >95% pure.

Anal. Calcd for C₂₇H₂₉F₅N₆O • 0.05 CHCl₃: C = 51.36, H = 4.63, N = 15.50. Found: C = 51.13, H = 4.63, N = 15.81.

25

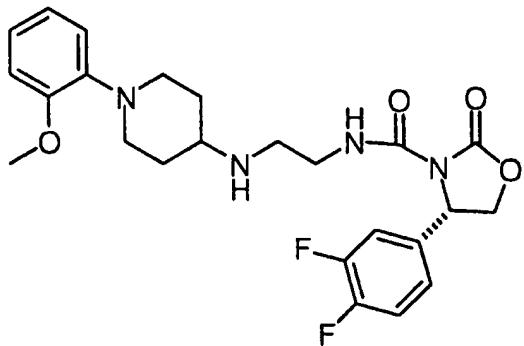
EXAMPLE 78



(4S)-4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-pyrimidinylpiperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester
 5 1¹H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16
 10 minutes, 2 ml/min flow rate) focus = 215 nm; 100% pure.
 Anal. Calcd for C₂₆H₃₁F₂N₇O₅ • 1.0 H₂O: C = 54.06, H = 5.76, N = 16.98. Found: C = 54.07, H = 5.53, N = 16.82.

EXAMPLE 79



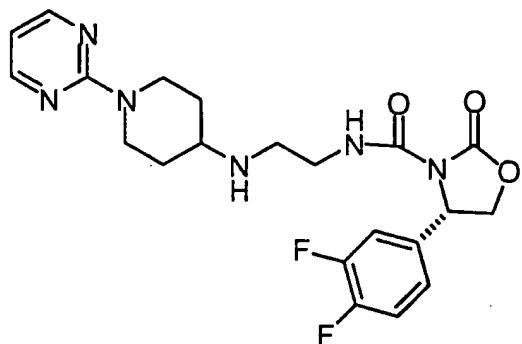
15

(4S)-4-(3,4-Difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid (2-(1-(2-methoxyphenyl)piperidin-4-ylamino)ethyl)amide
 11¹H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) focus = 215 nm; 100% pure.

Anal. Calcd for C₂₄H₂₈F₂N₄O₄ • 2.0 HCl, 1.65 H₂O, and 0.3 EtOAc: C = 50.14, H = 5.96, N = 9.28. Found: C = 50.12, H = 5.81, N = 9.27.

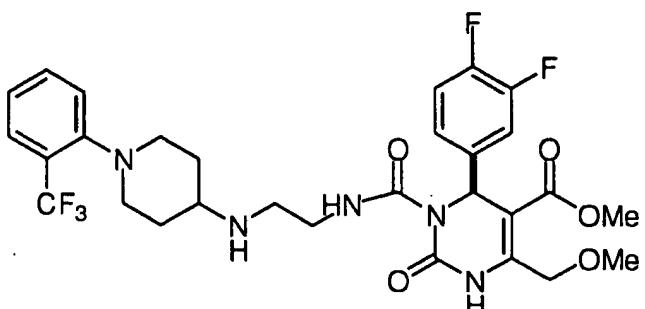
EXAMPLE 80



(4S)-4-(3,4-Difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid (2-(2-pyrimidinylpiperidin-4-ylamino)ethyl)amide
 10 1H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) focus = 215 nm; 98.4% pure.
 15 Anal. Calcd for C₂₁H₂₄F₂N₆O₃ • 3.0 HCl and 0.45 EtOAc: C = 45.98, H = 5.18, N = 14.11. Found: C = 45.68, H = 5.34, N = 14.13.

EXAMPLE 81



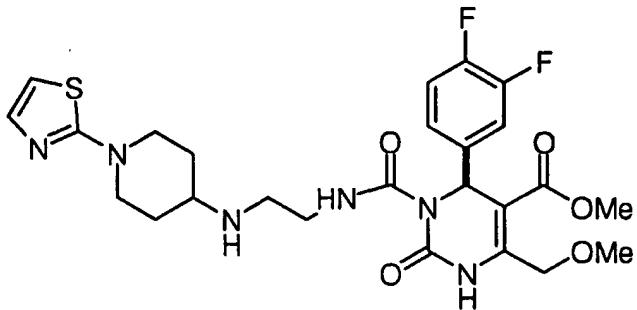
(4S)-4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(1-(2-trifluoromethylphenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester

5 ¹H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) focus = 215 nm; 95.2% pure.

10 Anal. Calcd for C₂₉H₃₂F₅N₅O₅ • 1.0 HCl and 1.6 H₂O: C = 50.41, H = 5.28, N = 10.14. Found: C = 50.38, H = 5.18, N = 10.36.

EXAMPLE 82



(4S)-4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-thiazolylpiperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester

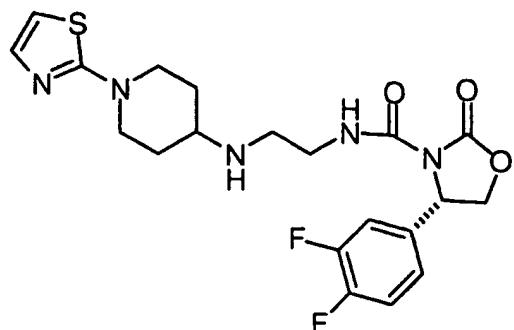
15 ¹H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

20 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) focus = 215 nm; 95.4% pure.

25 Anal. Calcd for C₂₅H₃₀F₂N₆O₅S • 0.15 CH₂Cl₂ and 0.25 Et₂O: C = 52.70, H = 5.55, N = 14.10. Found: C = 52.71, H = 5.53, N = 13.97.

25

EXAMPLE 83



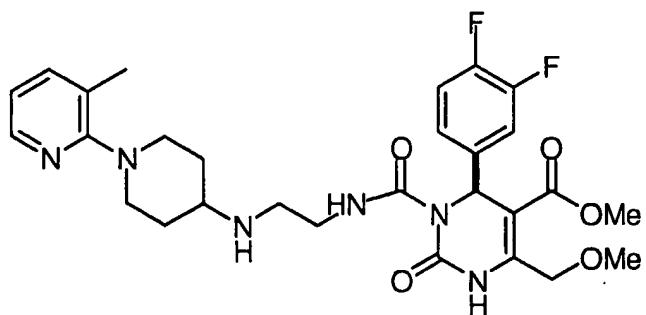
(4S)-4-(3,4-Difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid (2-(2-thiazolyl)piperidin-4-ylamino)ethyl)amide

5 ^1H NMR (CDCl_3 , 400 MHz) consistent with assigned structure.

HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H_2O [0.1% H_3PO_4] - CH_3CN , 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) focus = 215 nm; 98.3% pure.

10 Anal. Calcd for $\text{C}_{20}\text{H}_{23}\text{F}_2\text{N}_5\text{O}_3\text{S} \bullet 0.25\text{H}_2\text{O}$: C = 52.68, H = 5.19, N = 15.36. Found: C = 52.67, H = 5.28, N = 15.22.

EXAMPLE 84



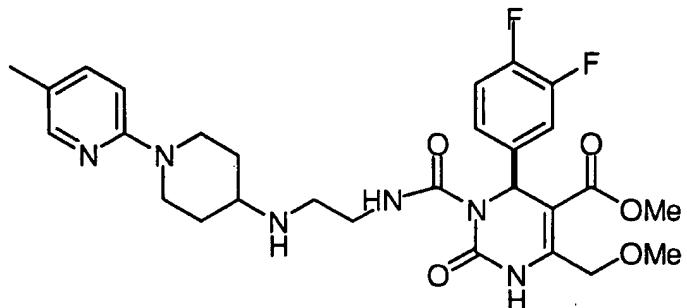
(4S)-4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(3-methylpyridyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester

15 ^1H NMR (CDCl_3 , 400 MHz) consistent with assigned structure.

HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) focus = 215 nm; 100% pure.

Anal. Calcd for C₂₈H₃₄F₂N₆O₅ • 0.15 CH₃Cl: C = 57.25, H = 5.83, N = 14.23. Found: C = 57.06, H = 5.68, N = 14.22.

EXAMPLE 85



(4S)-4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(5-methylpyridyl)piperidin-4-ylamino)ethylcarbamoyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester

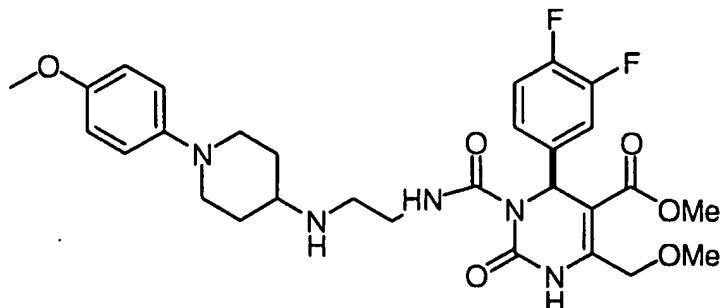
¹H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) focus = 215 nm; 97.3% pure.

Anal. Calcd for C₂₈H₃₄F₂N₆O₅ • 0.30 CH₃Cl: C = 55.86, H = 5.68, N = 13.81. Found: C = 55.71, H = 5.56, N = 14.15.

20

EXAMPLE 86



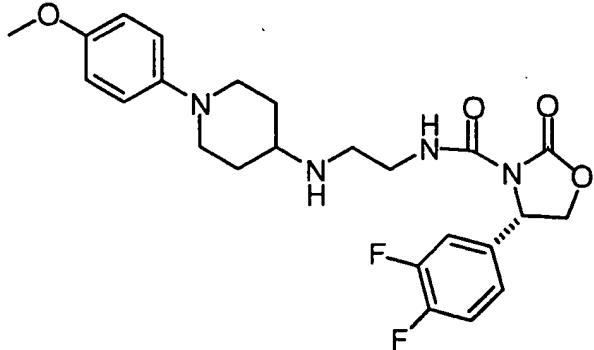
(4S)-4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(1-(4-methoxyphenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester

1H NMR (CDCl₃, 400 MHz) consistent with assigned
5 structure.

HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) focus = 215 nm; >95% pure.

Anal. Calcd for C₂₉H₃₅F₂N₅O₆ • 2.0 HCl, 1.1 H₂O, and 0.55
10 Et₂O: C = 51.96, H = 6.25, N = 9.71. Found: C = 51.96, H = 5.97, N = 9.72.

EXAMPLE 87



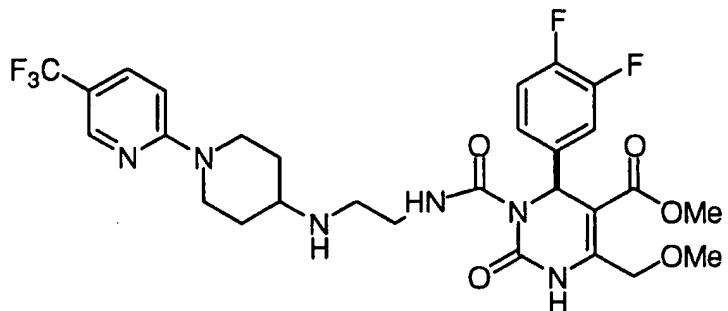
(4S)-4-(3,4-Difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid (2-(1-(4-methoxyphenyl)piperidin-4-ylamino)ethyl)amide

15 1H NMR (CDCl₃, 400 MHz) consistent with assigned
structure.

HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16
20 minutes, 2 ml/min flow rate) focus = 215 nm; >95% pure.

Anal. Calcd for C₂₄H₂₈F₂N₄O₄ • 2.0 HCl, 1.7 H₂O, and 0.4 Et₂O: C = 50.52, H = 6.21, N = 9.21. Found: C = 50.54, H = 5.82, N = 9.12.

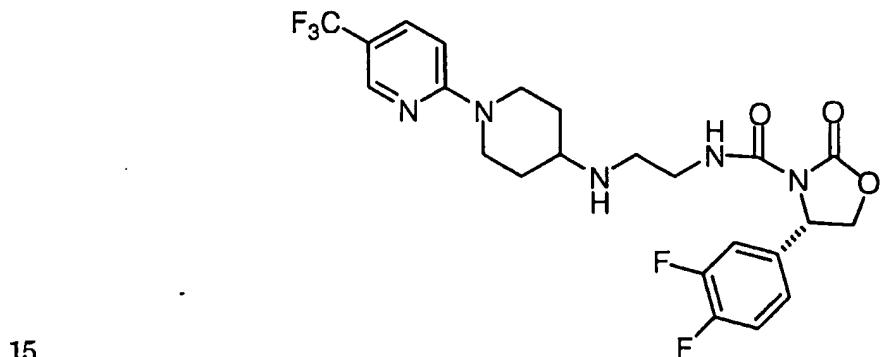
EXAMPLE 88



(4S)-4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(5-trifluoromethylpyridyl)piperidin-4-ylamino)ethylcarbamoyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester
 5 1H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

10 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) focus = 215 nm; 95.2% pure.
 Anal. Calcd for C₂₄H₂₈F₂N₄O₄ • 1.45 TFA: C = 46.86, H = 4.13, N = 10.61. Found: C = 46.90, H = 3.76, N = 10.91.

EXAMPLE 89

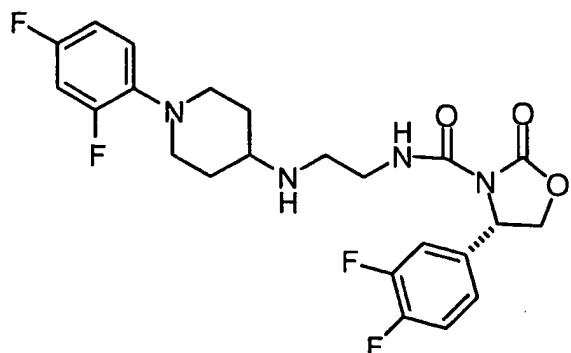


15 (4S)-4-(3,4-Difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid (2-(2-(5-trifluoromethylpyridyl)piperidin-4-ylamino)ethyl)amide
1H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) focus = 215 nm; 96.8% pure.

Anal. Calcd for C₂₄H₂₈F₂N₄O₄ • 1.25 TFA and 0.95 H₂O: C = 45.50, H = 4.07, N = 10.41. Found: C = 45.34, H = 3.72, N = 10.80.

EXAMPLE 90



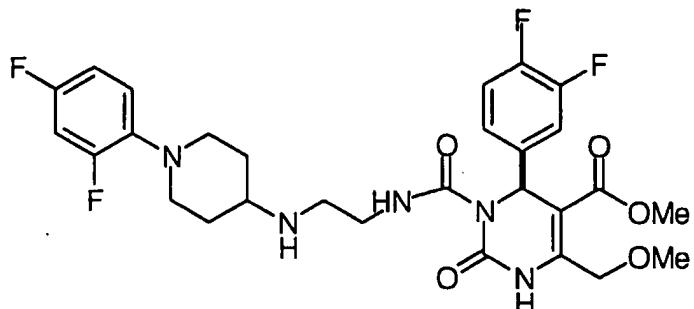
10 (4S)-4-(3,4-Difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid (2-(2-(2,4-difluorophenyl)piperidin-4-ylamino)ethyl)amide

15 ¹H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

10 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) focus = 215 nm; 100% pure.

15 Anal. Calcd for C₂₃H₂₄F₄N₄O₃ • 1.40 HCl: C = 51.97, H = 4.82, N = 10.54. Found: C = 52.02, H = 4.90, N = 10.71.

EXAMPLE 91



(4S)-4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(1-(2,4-difluorophenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester

^1H NMR (CDCl₃, 400 MHz) consistent with assigned

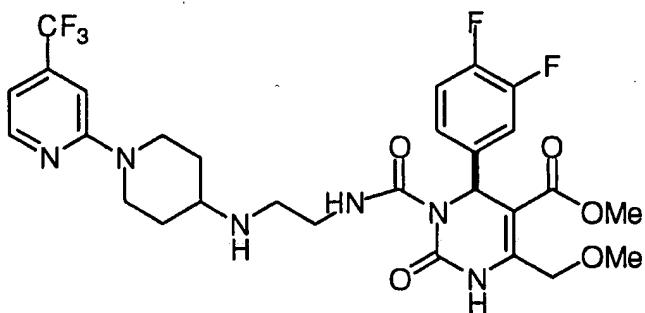
5 structure.

HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) focus = 215 nm; 100% pure.

Anal. Calcd for C₂₈H₃₁F₄N₅O₅ • 1.30 HCl: C = 52.46, H =

10 5.08, N = 10.93. Found: C = 52.42, H = 5.18, N = 10.76.

EXAMPLE 92



(4S)-4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(4-trifluoromethylpyridyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester

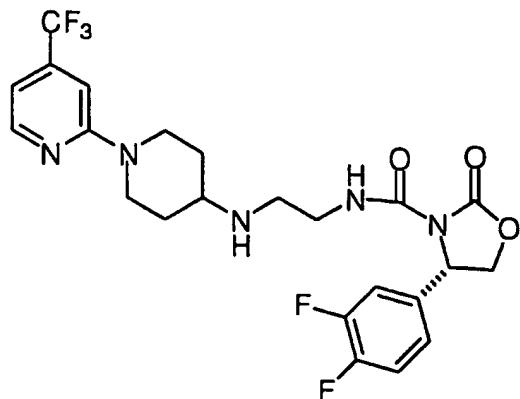
^1H NMR (CDCl₃, 400 MHz) consistent with assigned

structure.

HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) focus = 215 nm; 95.7% pure.

Anal. Calcd for C₂₈H₃₁F₅N₆O₅ • 0.15 CH₂Cl₂: C = 52.88, H = 4.93, N = 13.15. Found: C = 53.04, H = 4.98, N = 12.77.

EXAMPLE 93



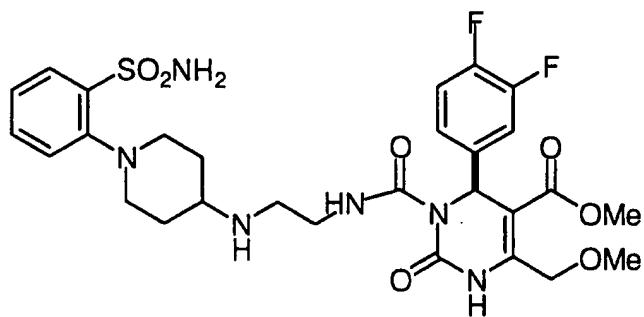
(4S)-4-(3,4-Difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid (2-(2-(4-trifluoromethylpyridyl)piperidin-4-ylamino)ethyl)amide

5 ^1H NMR (CDCl_3 , 400 MHz) consistent with assigned structure.

HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H_2O [0.1% H_3PO_4] - CH_3CN , 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) focus = 215 nm; 100% pure.

10 FABLRMS m/e 514.08 g/mole (M^++H , $\text{C}_{23}\text{H}_{24}\text{F}_5\text{N}_5\text{O}_3$ = 513.46 g/mole.)

EXAMPLE 94



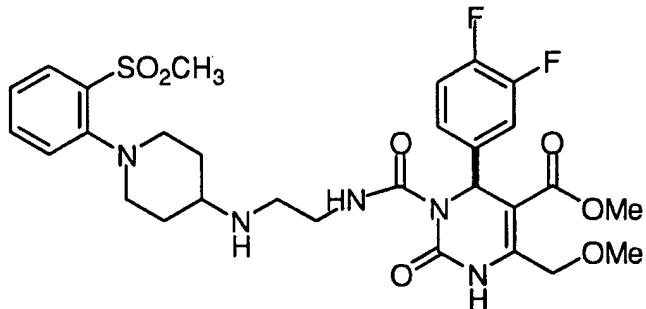
15 (4S)-4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(1-(2-sulfonamidophenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester

¹H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

FABLRMS m/e 637 g/mole (M⁺+H, C₂₈H₃₄F₂N₆O₇S = 636.676 g/mole.)

5 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) focus = 215 nm; 98.8% pure.

EXAMPLE 95



10

(4S)-4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(1-(2-methanesulfonylphenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester

15 ¹H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

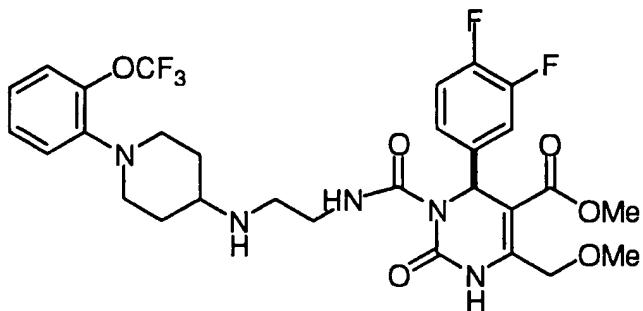
FABLRMS m/e 635 g/mole (M⁺+H, C₂₉H₃₄F₂N₅O₇S = 634.68 g/mole.)

16 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) focus = 215 nm; 96.1% pure.

Anal. Calcd for C₂₉H₃₄F₂N₅O₇S • 0.95 HCl: C = 51.69, H =

5.30, N = 10.39. Found: C = 51.67, H = 5.31, N = 10.05.

EXAMPLE 96



(4S)-4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(1-(2-trifluormethylphenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-

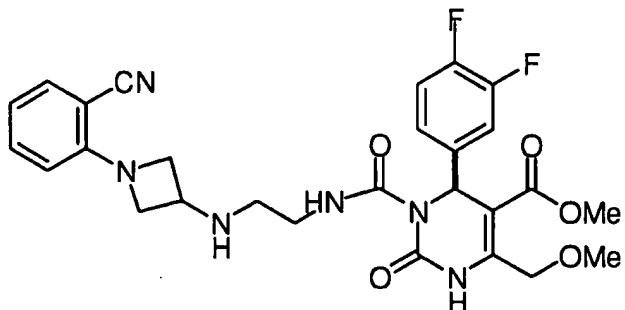
5 tetrahydropyrimidine-5-carboxylic acid methyl ester

1H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

FABLRMS m/e 642 g/mole (M⁺+H, C₂₉H₃₂F₅N₅O₆ = 641.596 g/mole.)

10 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) focus = 215 nm; 100% pure.

EXAMPLE 97



15

(4S)-4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(1-(2-cyanophenyl)azetidin-3-ylamino)ethylcarbamoyl)-1,2,3,4-

tetrahydropyrimidine-5-carboxylic acid methyl ester

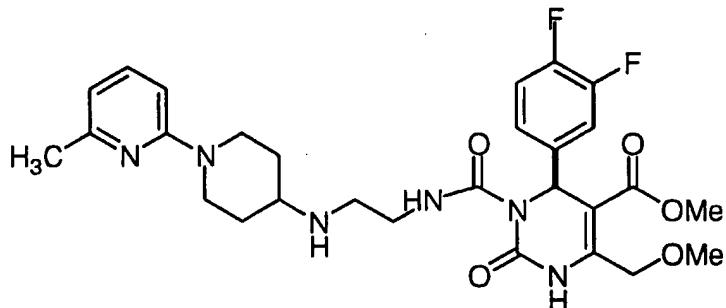
1H NMR (CDCl₃, 400 MHz) consistent with assigned

20 structure.

FABLRMS m/e 554 g/mole (M⁺+H, C₂₇H₂₇F₂N₆O₅ = 553.547 g/mole.)

HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 5 minutes, 2 ml/min flow rate) focus = 215 nm; 96% pure.

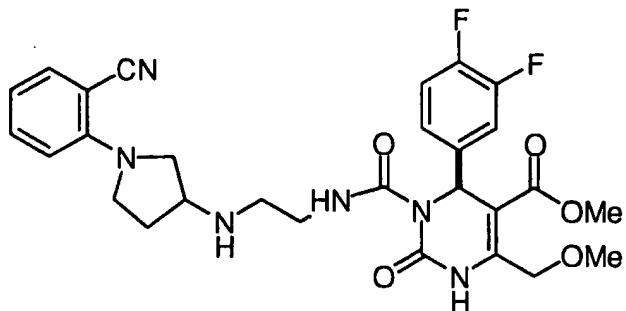
EXAMPLE 98



(4S)-4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(6-methylpyridinyl)piperidin-4-ylamino)ethylcarbamoyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester
10
15 ¹H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

FABLRMS m/e 573 g/mole (M⁺+H, C₂₈H₃₄F₂N₆O₅ = 572.62 g/mole.)
HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) focus = 215 nm; 95% pure.

EXAMPLE 99



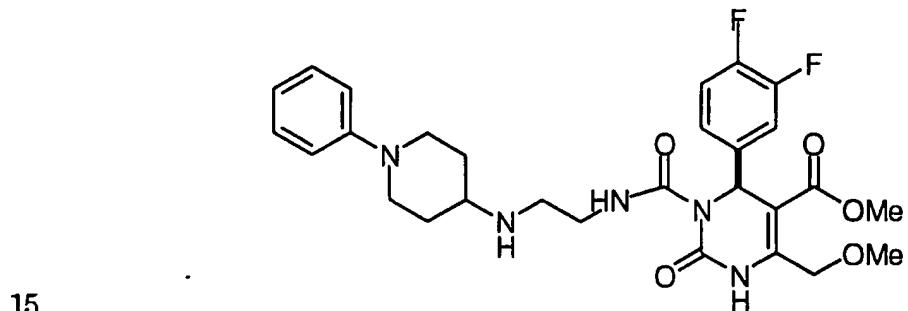
5 **(4S)-4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(1-(2-cyanophenyl)pyrrolodin-3-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester**

10 ^1H NMR (CDCl_3 , 400 MHz) consistent with assigned structure.

FABLRMS m/e 569 g/mole (M^++H , $\text{C}_{28}\text{H}_{30}\text{F}_2\text{N}_6\text{O}_5 = 568.582$ g/mole.)

15 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H_2O [0.1% H_3PO_4] - CH_3CN , 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) focus = 215 nm; 98% pure.

EXAMPLE 100



15

(4S)-4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(1-(phenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester

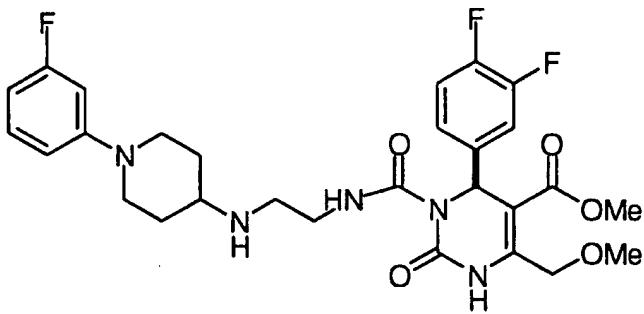
¹H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

FABLRMS m/e 558 g/mole (M⁺+H, C₂₈H₃₃F₂N₅O₅ = 557.599 g/mole.)

5 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) focus = 215 nm; 100% pure.

EXAMPLE 101

10



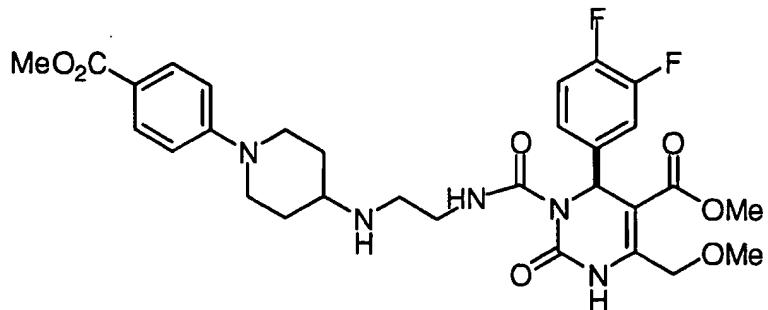
(4S)-4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(1-(3-fluorophenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester

15 ¹H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

FABLRMS m/e 576 g/mole (M⁺+H, C₂₈H₃₂F₃N₅O₅ = 575.589 g/mole.)

17 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) focus = 215 nm; 98% pure.

EXAMPLE 102

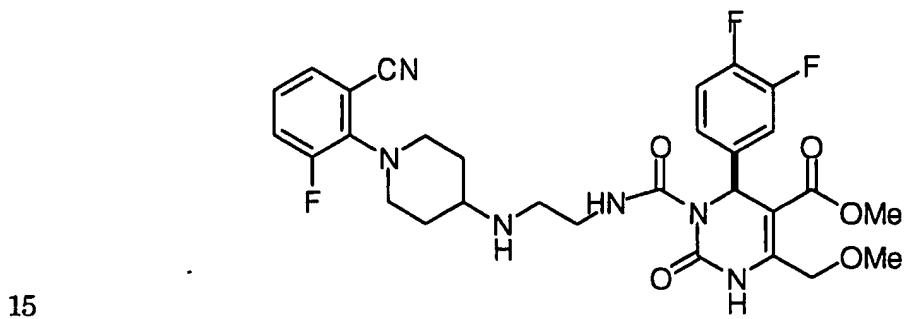


(4S)-4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(1-(4-carboxymethylphenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester
 5 1H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

FABLRMS m/e 616 g/mole (M⁺+H, C₃₀H₃₅F₂N₅O₇ = 615.635 g/mole.)

10 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) focus = 215 nm; >99% pure.

EXAMPLE 103



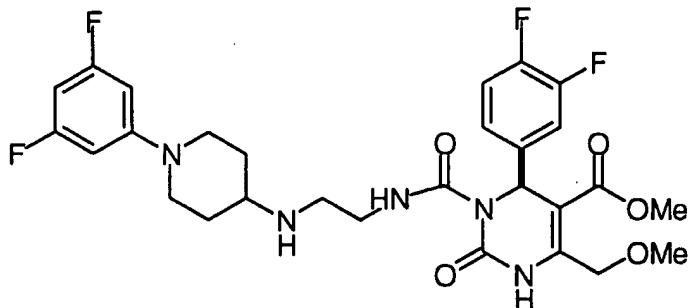
15 (4S)-4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(1-(2-cyano-6-fluorophenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester

¹H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

FABLRMS m/e 601 g/mole (M⁺⁺H, C₂₉H₃₁F₃N₆O₅ = 600.603 g/mole.)

5 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) focus = 215 nm; 98.7% pure.

EXAMPLE 104



10

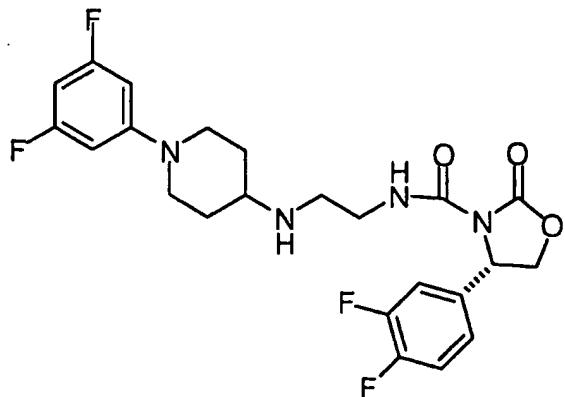
(4S)-4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(1-(3,5-difluorophenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester

15 ¹H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

FABLRMS m/e 594 g/mole (M⁺⁺H, C₂₈H₃₁F₄N₅O₅ = 593.583 g/mole.)

20 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) focus = 215 nm; 97.8% pure.

EXAMPLE 105



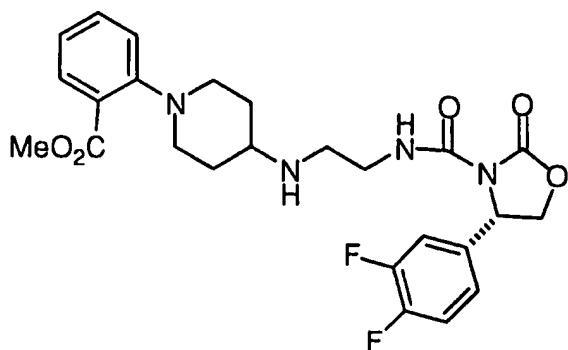
(4S)-4-(3,4-Difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid (2-(1-(3,5-difluorophenyl)piperidin-4-ylamino)ethyl)amide

5 ^1H NMR (CDCl_3 , 400 MHz) consistent with assigned structure.

FABLRMS m/e 481 g/mole (M^++H , $\text{C}_{23}\text{H}_{24}\text{F}_4\text{N}_4\text{O}_3 = 480.463$ g/mole.)

10 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H_2O [0.1% H_3PO_4] - CH_3CN , 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) focus = 215 nm; 97.1% pure.

EXAMPLE 106



15 (4S)-4-(3,4-Difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid (2-(1-(2-carboxymethylphenyl)piperidin-4-ylamino)ethyl)amide

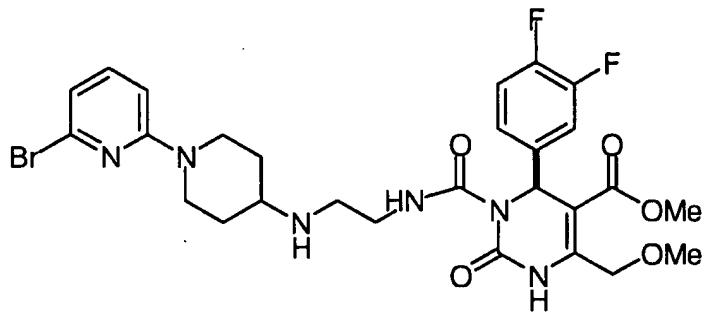
¹H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

FABLRMS m/e 503 g/mole (M⁺+H, C₂₅H₂₈F₂N₄O₅ = 502.523 g/mole.)

5 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) focus = 215 nm; 99.5% pure.

EXAMPLE 107

10



10

(4S)-4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-(6-bromopyridyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester

15

¹H NMR (CDCl₃, 400 MHz) consistent with assigned

structure.

FABLRMS m/e 637 g/mole (M⁺+H, C₂₇H₃₁F₂N₆O₅ = 637.486 g/mole.)

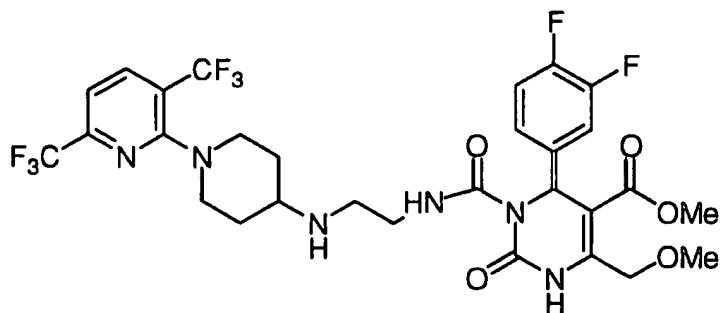
15

HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16

20

minutes, 2 ml/min flow rate) focus = 215 nm; 99.4% pure.

EXAMPLE 108



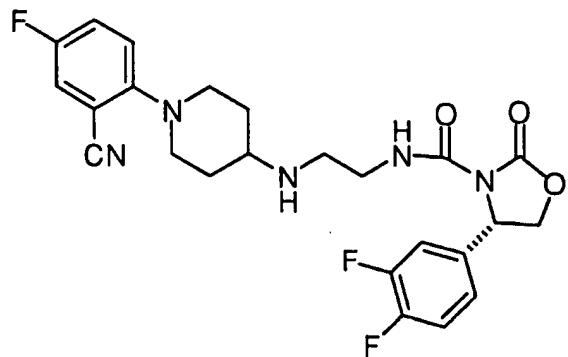
5 (4S)-4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-(3,6-bistrifluoromethylpyridyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester

10 ^1H NMR (CDCl_3 , 400 MHz) consistent with assigned structure.

FABLRMS m/e 695 g/mole (M^++H , $\text{C}_{29}\text{H}_{30}\text{F}_8\text{N}_6\text{O}_5 = 694.587$ g/mole.)

15 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H_2O [0.1% H_3PO_4] - CH_3CN , 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) focus = 215 nm; 95.3% pure.

EXAMPLE 109



15

(4S)-4-(3,4-Difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid (2-(1-(2-cyano-4-fluorophenyl)piperidin-4-ylamino)ethyl)amide

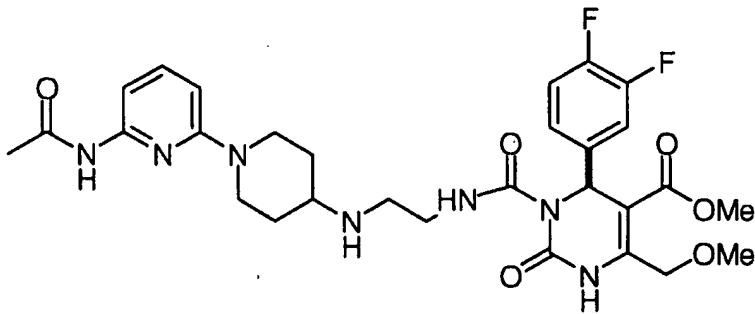
¹H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

FABLRMS m/e 488 g/mole (M⁺+H, C₂₄H₂₄F₂N₅O₃ = 487.485 g/mole.)

5 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) focus = 215 nm; 99.3% pure.

EXAMPLE 110

10



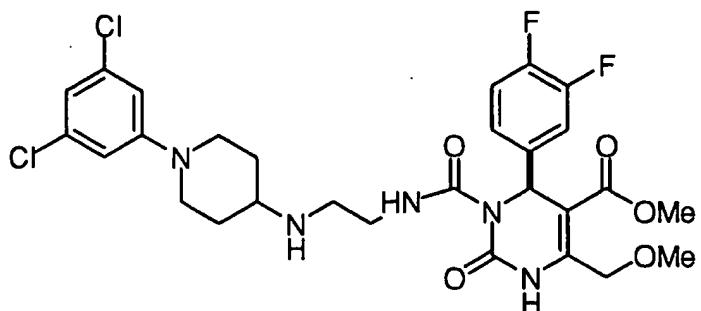
(4S)-4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(6-N-acetylaminopyridyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester

15 ¹H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

FABLRMS m/e 615 g/mole (M⁺+H, C₃₀H₃₆F₂N₆O₆ = 614.65 g/mole.)

20 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) focus = 215 nm; 99.2% pure.

EXAMPLE 111



(4S)-4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-(3,5-dichlorophenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-

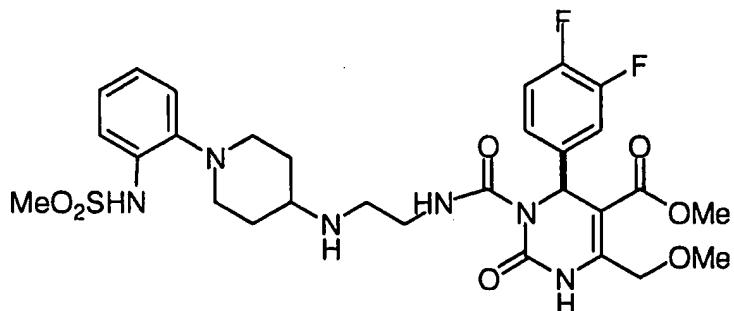
5 **tetrahydropyrimidine-5-carboxylic acid methyl ester**

1H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

FABLRMS m/e 626 g/mole (M⁺+H, C₂₈H₃₁Cl₂F₂N₅O₅ = 626.489 g/mole.)

10 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) focus = 215 nm; 96.4% pure.

EXAMPLE 112



15

(4S)-4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-(2-N-methanesulfonylaminophenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester

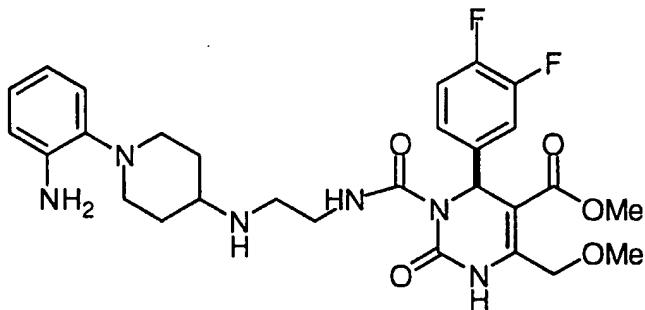
¹H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

FABLRMS m/e 651 g/mole (M⁺⁺H, C₂₉H₃₆F₂N₆O₇S = 650.709 g/mole.)

5 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) focus = 215 nm; 100% pure.

EXAMPLE 113

10



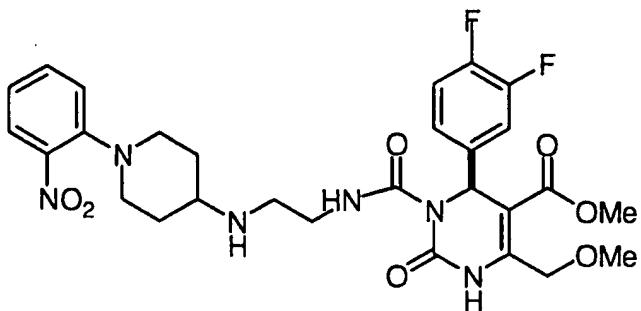
(4S)-4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-aminophenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester

15 ¹H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

FABLRMS m/e 573 g/mole (M⁺⁺H, C₂₈H₃₄F₂N₆O₅ = 572.617 g/mole.)

20 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) focus = 215 nm; 100% pure.

EXAMPLE 114



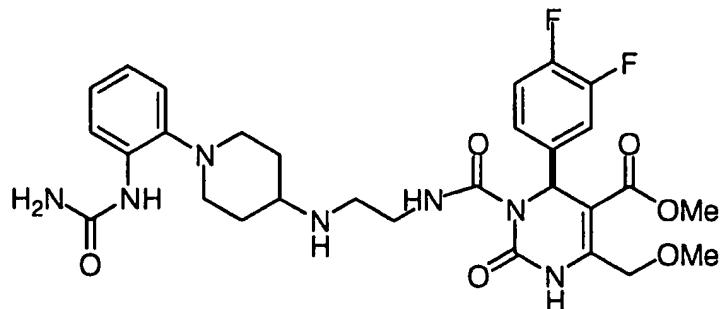
(4S)-4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-nitrophenyl)piperidin-4-ylamino)ethylcarbamoyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester

5 ¹H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

FABLRMS m/e 617 g/mole (M⁺+H, C₂₉H₃₄F₂N₆O₇ = 616.629 g/mole.)

10 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) focus = 215 nm; 100% pure.

EXAMPLE 115



15

(4S)-4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-N-carboxamidoaminophenyl)piperidin-4-ylamino)ethylcarbamoyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester

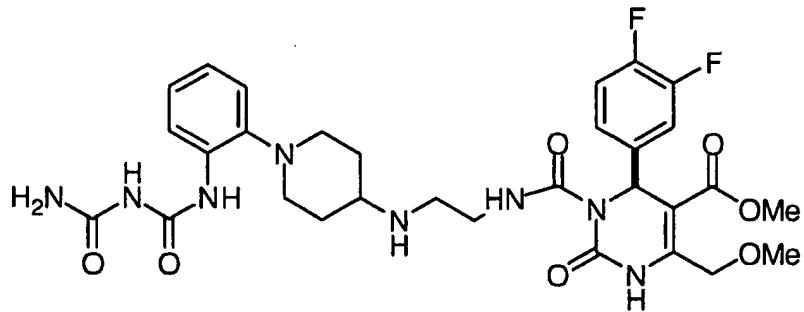
¹H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

FABLRMS m/e 616 g/mole (M⁺+H, C₂₉H₃₅F₂N₇O₆ = 615.644 g/mole.)

5 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) focus = 215 nm; 98.4% pure.

EXAMPLE 116

10



(4S)-4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-(2-N-1-imidocarbonic diamidyl)phenyl)piperidin-4-ylamino)ethylcarbamoyl)-
1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester

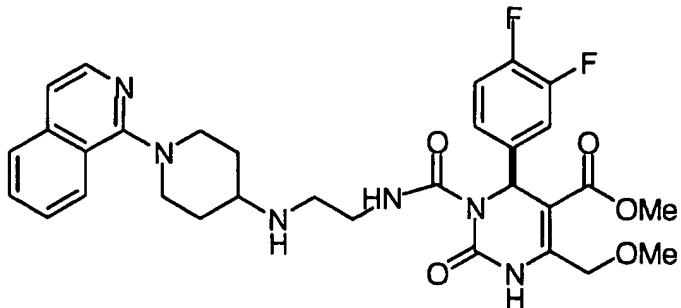
15

structure.

FABLRMS m/e 659 g/mole (M⁺+H, C₃₀H₃₆F₂N₈O₇ = 658.66 g/mole.)

17 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) focus = 215 nm; 96.9% pure.

EXAMPLE 117



(4S)-4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-(1-isoquinolinyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-

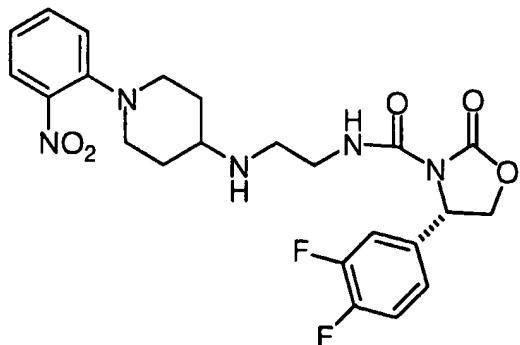
5 tetrahydropyrimidine-5-carboxylic acid methyl ester

1H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

FABLRMS m/e 609 g/mole (M⁺⁺H, C₃₁H₃₄F₂N₆O₅ = 608.651 g/mole.)

10 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) focus = 215 nm; 95% pure.

EXAMPLE 118



15

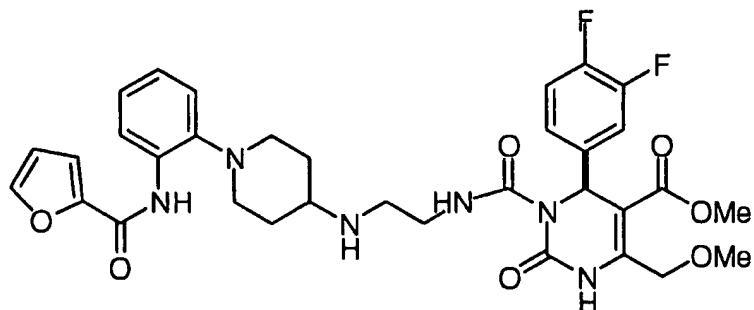
(4S)-4-(3,4-Difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid (2-(1-(2-nitrophenyl)piperidin-4-ylamino)ethyl)amide

1H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

FABLRMS m/e 504 g/mole (M⁺+H, C₂₄H₂₇F₂N₅O₅ = 503.510 g/mole.)

HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 5 minutes, 2 ml/min flow rate) focus = 215 nm; 100% pure.

EXAMPLE 119

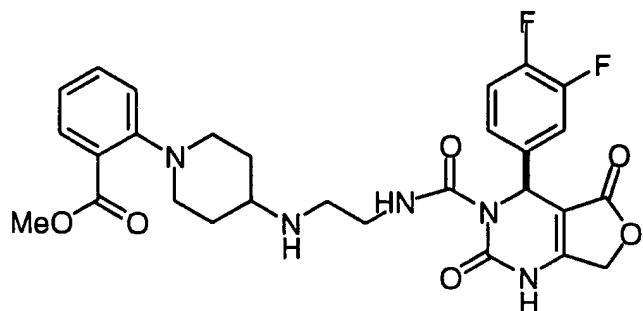


(4S)-4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-N-(2-furanyl)carbonylaminophenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester
10 ¹H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

FABLRMS m/e 667 g/mole (M⁺+H, C₃₂H₃₆F₂N₆O₇ = 608.651 g/mole.)

HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) focus = 215 nm; 99% pure.

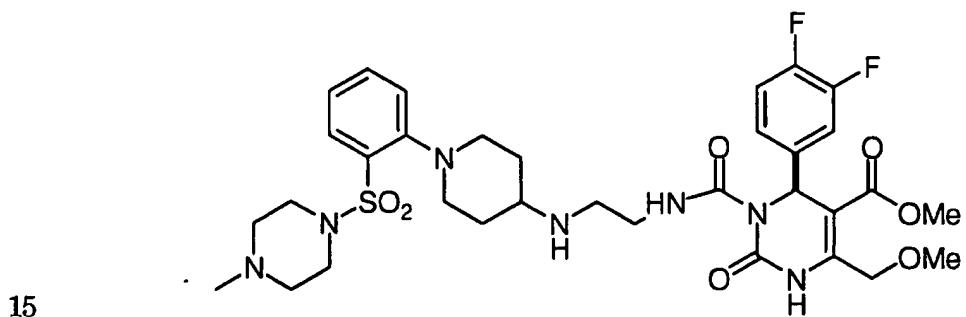
EXAMPLE 120



(4S)-4-(3,4-Difluorophenyl)-2-oxo-3-(2-(2-(2-arboxymethylphenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydro-4H-furo[3,4-d]pyrimidine
 5 **1**¹H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

FABLRMS m/e 570 g/mole (M⁺+H, C₂₈H₂₉F₂N₅O₆ = 569.571 g/mole.)
 10 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) focus = 215 nm; 97.9% pure.

EXAMPLE 121



(4S)-4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-(4-N-methylpiperazinyl)sulfonylphenyl)piperidin-4-ylamino)ethylcarbamoyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester
 15

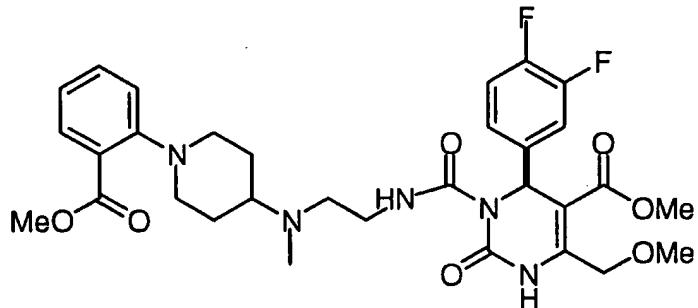
¹H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

FABLRMS m/e 720 g/mole (M⁺+H, C₃₃H₄₃F₂N₇O₇S = 719.816 g/mole.)

5 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) focus = 215 nm; 98.5% pure.

EXAMPLE 122

10



(4S)-4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-carboxymethylphenyl)piperidin-4-yl-1-methylamino)ethylcarbamoyl)-
1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester

15

¹H NMR (CDCl₃, 400 MHz) consistent with assigned

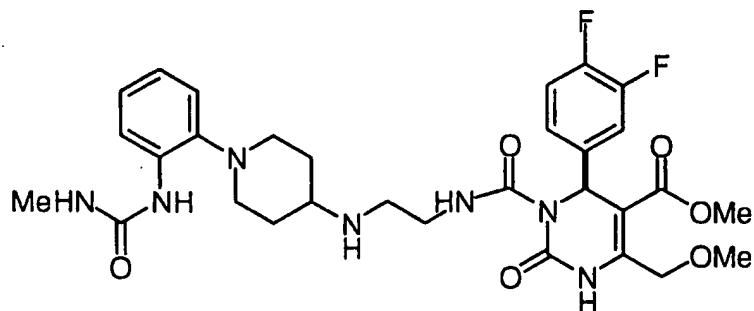
structure.

FABLRMS m/e 630 g/mole (M⁺+H, C₃₁H₃₇F₂N₅O₇ = 629.662 g/mole.)

20

HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) focus = 215 nm; 97.3% pure.

EXAMPLE 123



(4S)-4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(1-N-(3-N-methylureyl)phenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-

5 tetrahydropyrimidine-5-carboxylic acid methyl ester

1H NMR (CDCl₃, 400 MHz) consistent with assigned structure.

FABLRMS m/e 630 g/mole (M⁺+H, C₃₀H₃₇F₂N₇O₆ = 629.669 g/mole.)

10 HPLC (Vydac; C18; diameter = 4.6 mm; length = 150 mm; gradient = H₂O [0.1% H₃PO₄] - CH₃CN, 95% - 5%, 5% - 95%, over 16 minutes, 2 ml/min flow rate) focus = 215 nm; 100% pure.

EXAMPLE 124

15

As a specific embodiment of an oral composition, 100 mg of the compound of Example 9 is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size O hard gel capsule.

20

EXAMPLE 125

Screening assay: Alpha 1a Adrenergic Receptor Binding

25 Membranes prepared from the stably transfected human alpha 1a cell line (ATCC CRL 11140) were used to identify compounds that bind to the human alpha 1a adrenergic receptor. These competition binding reactions (total volume = 200 μ l) contained 50 mM Tris-HCl pH.

7.4, 5 mM EDTA, 150 mM NaCl, 100 pM [¹²⁵I]-HEAT, membranes prepared from the alpha 1a cell line and increasing amounts of unlabeled ligand. Reactions were incubated at room temperature for one hour with shaking. Reactions were filtered onto Whatman GF/C 5 glass fiber filters with a Inotec 96 well cell harvester. Filters were washed three times with ice cold buffer and bound radioactivity was determined (Ki). Representative compounds of the present invention were found to have Ki values \leq 50 nM.

10

EXAMPLE 126

Selective Binding assays

Membranes prepared from stably transfected human alpha 1d and alpha 1b cell lines (ATCC CRL 11138 and CRL 11139, respectively) 15 were used to identify compounds that selectively bind to the human alpha 1a adrenergic receptor. These competition binding reactions (total volume = 200 μ l) contained 50 mM Tris-HCl pH. 7.4, 5 mM EDTA, 150 mM NaCl, 100 pM [¹²⁵I]-HEAT, membranes prepared from cell lines transfected with the respective alpha 1 subtype expression plasmid and 20 increasing amounts of unlabeled ligand. Reactions were incubated at room temperature for one hour with shaking. Reactions were filtered onto Whatman GF/C glass fiber filters with a Inotec 96 well cell harvester. Filters were washed three times with ice cold buffer and bound radioactivity was determined (Ki).

25

EXAMPLE 127

EXEMPLARY COUNTERSCREENS

30 1. Assay Title: Dopamine D2, D3, D4 in vitro screen

The objective of this assay is to eliminate agents which specifically affect binding of [³H] spiperone to cells expressing human dopamine receptors D2, D3 or D4.

Method:

Modified from VanTol et al (1991); Nature (Vol 350) Pg 610-613.

5 Frozen pellets containing specific dopamine receptor subtypes stably expressed in clonal cell lines are lysed in 2 ml lysing buffer (10mM Tris-HCl/5mM Mg, pH 7.4). Pellets obtained after centrifuging these membranes (15' at 24,450 rpm) are resuspended in 50mM Tris-HCl pH 7.4 containing EDTA, MgCl₂, KCl, NaCl, CaCl₂
10 and ascorbate to give a 1 Mg/mL suspension. The assay is initiated by adding 50-75 µg membranes in a total volume of 500 µl containing 0.2 nM [³H]-spiperone. Non-specific binding is defined using 10 µM apomorphine. The assay is terminated after a 2 hour incubation at room temperature by rapid filtration over GF/B filters presoaked in 0.3%
15 PEI, using 50mM Tris-HCl pH 7.4.

2. Assay Title: Serotonin 5HT1a

20 The objective of this assay is to eliminate agents which specifically affect binding to cloned human 5HT1a receptor

Method:

Modified from Schelegel and Peroutka Biochemical Pharmacology 35: 1943-1949 (1986).

25 Mammalian cells expressing cloned human 5HT1a receptors are lysed in ice-cold 5 mM Tris-HCl, 2 mM EDTA (pH 7.4) and homogenized with a polytron homogenizer. The homogenate is centrifuged at 1000Xg for 30', and then the supernatant is centrifuged again at 38,000Xg for 30'. The binding assay contains 0.25 nM [³H]8-OH-
30 DPAT (8-hydroxy-2-dipropylamino-1,2,3,4-tetrahydronaphthalene) in 50 mM Tris-HCl, 4 mM CaCl₂ and 1mg/ml ascorbate. Non-specific binding is defined using 10 µM propranolol. The assay is terminated after a 1 hour incubation at room temperature by rapid filtration over GF/Cfilters

EXAMPLE 128

EXEMPLARY FUNCTIONAL ASSAYS

In order to confirm the specificity of compounds for the

5 human alpha 1a adrenergic receptor and to define the biological activity
of the compounds, the following functional tests may be performed:

1. In vitro Rat, Dog and Human Prostate and Dog Urethra

Taconic Farms Sprague-Dawley male rats, weighing 250-

10 400 grams are sacrificed by cervical dislocation under anesthesia (methohexitol; 50 mg/kg, i.p.). An incision is made into the lower abdomen to remove the ventral lobes of the prostate. Each prostate removed from a mongrel dog is cut into 6-8 pieces longitudinally along the urethra opening and stored in ice-cold oxygenated Krebs solution

15 overnight before use if necessary. Dog urethra proximal to prostate is cut into approximately 5 mm rings, the rings are then cut open for contractile measurement of circular muscles. Human prostate chips from transurethral surgery of benign prostate hyperplasia are also stored overnight in ice-cold Krebs solution if needed.

20 The tissue is placed in a Petri dish containing oxygenated Krebs solution [NaCl, 118 mM; KCl, 4.7 mM; CaCl₂, 2.5 mM; KH₂PO₄, 1.2 mM; MgSO₄, 1.2 mM; NaHCO₃, 2.0 mM; dextrose, 11 mM] warmed to 37°C. Excess lipid material and connective tissue are carefully removed. Tissue segments are attached to glass tissue holders with 4-0 surgical silk and placed in a 5 ml jacketed tissue bath containing Krebs buffer at 37°C, bubbled with 5% CO₂/95% O₂. The tissues are connected to a Statham-Gould force transducer; 1 gram (rat, human) or 1.5 gram (dog) of tension is applied and the tissues are allowed to equilibrate for one hour. Contractions are recorded on a Hewlett-Packard 7700 series strip chart recorder.

25 After a single priming dose of 3 µM (for rat), 10 µM (for dog) and 20 µM (for human) of phenylephrine, a cumulative concentration response curve to an agonist is generated; the tissues are washed every 10 minutes for one hour. Vehicle or antagonist is added to the bath and

30

allowed to incubate for one hour, then another cumulative concentration response curve to the agonist is generated.

EC₅₀ values are calculated for each group using GraphPad Inplot software. pA₂ (-log K_b) values were obtained from Schild plot

5 when three or more concentrations were tested. When less than three concentrations of antagonist are tested, K_b values are calculated according to the following formula K_b = $\frac{1}{[B]}$,

x-1

10 where x is the ratio of EC₅₀ of agonist in the presence and absence of antagonist and [B] is the antagonist concentration.

2. Measurement of Intra-Urethral Pressure in Anesthetized Dogs

PURPOSE: Benign prostatic hyperplasia causes a decreased urine flow
15 rate that may be produced by both passive physical obstruction of the prostatic urethra from increased prostate mass as well as active obstruction due to prostatic contraction. Alpha adrenergic receptor antagonists such as prazosin and terazosin prevent active prostatic contraction, thus improve urine flow rate and provide symptomatic
20 relief in man. However, these are non-selective alpha 1 receptor antagonists which also have pronounced vascular effects. Because we have identified the alpha 1a receptor subtype as the predominant subtype in the human prostate, it is now possible to specifically target this receptor to inhibit prostatic contraction without concomitant changes in
25 the vasculature. The following model is used to measure adrenergically mediated changes in intra-urethral pressure and arterial pressure in anesthetized dogs in order to evaluate the efficacy and potency of selective alpha adrenergic receptor antagonists. The goals are to: 1) identify the alpha 1 receptor subtypes responsible for prostatic/urethral
30 contraction and vascular responses, and 2) use this model to evaluate novel selective alpha adrenergic antagonists. Novel and standard alpha adrenergic antagonists may be evaluated in this manner.

METHODS: Male mongrel dogs (7-12 kg) are used in this study. The
35 dogs are anesthetized with pentobarbital sodium (35 mg/kg, i.v. plus 4

mg/kg/hr iv infusion). An endotracheal tube is inserted and the animal ventilated with room air using a Harvard instruments positive displacement large animal ventilator. Catheters (PE 240 or 260) are placed in the aorta via the femoral artery and vena cava via the femoral veins (2 catheters, one in each vein) for the measurement of arterial pressure and the administration of drugs, respectively. A supra-pubic incision ~1/2 inch lateral to the penis is made to expose the ureters, bladder and urethra. The ureters are ligated and cannulated so that urine flows freely into beakers. The dome of the bladder is retracted to facilitate dissection of the proximal and distal urethra. Umbilical tape is passed beneath the urethra at the bladder neck and another piece of umbilical tape is placed under the distal urethra approximately 1-2 cm distal to the prostate. The bladder is incised and a Millar micro-tip pressure transducer is advanced into the urethra. The bladder incision is sutured with 2-0 or 3-0 silk (purse-string suture) to hold the transducer. The tip of the transducer is placed in the prostatic urethra and the position of the Millar catheter is verified by gently squeezing the prostate and noting the large change in urethral pressure.

Phenylephrine, an alpha 1 adrenergic agonist, is administered (0.1-100 ug/kg, iv; 0.05 ml/kg volume) in order to construct dose response curves for changes in intra-urethral and arterial pressure. Following administration of increasing doses of an alpha adrenergic antagonist (or vehicle), the effects of phenylephrine on arterial pressure and intra-urethral pressure are re-evaluated. Four or five phenylephrine dose-response curves are generated in each animal (one control, three or four doses of antagonist or vehicle). The relative antagonist potency on phenylephrine induced changes in arterial and intra-urethral pressure are determined by Schild analysis. The family of averaged curves are fit simultaneously (using ALLFIT software package) with a four parameter logistic equation constraining the slope, minimum response, and maximum response to be constant among curves. The dose ratios for the antagonist doses (rightward shift in the dose-response curves from control) are calculated as the ratio of the ED50's for the respective curves. These dose-ratios are then used to construct a Schild plot and the Kb (expressed as ug/kg, iv) determined.

The Kb (dose of antagonist causing a 2-fold rightward shift of the phenylephrine dose-response curve) is used to compare the relative potency of the antagonists on inhibiting phenylephrine responses for intra-urethral and arterial pressure. The relative selectivity is

5 calculated as the ratio of arterial pressure and intra-urethral pressure Kb's. Effects of the alpha 1 antagonists on baseline arterial pressure are also monitored. Comparison of the relative antagonist potency on changes in arterial pressure and intra-urethral pressure provide insight as to whether the alpha receptor subtype responsible for

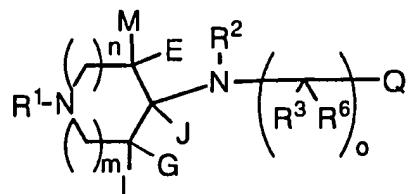
10 increasing intra-urethral pressure is also present in the systemic vasculature. According to this method, one is able to confirm the selectivity of alpha 1a adrenergic receptor antagonists that prevent the increase in intra-urethral pressure to phenylephrine without any activity at the vasculature.

15 While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual variations, adaptations and/or modifications as come within the scope of the following claims and their

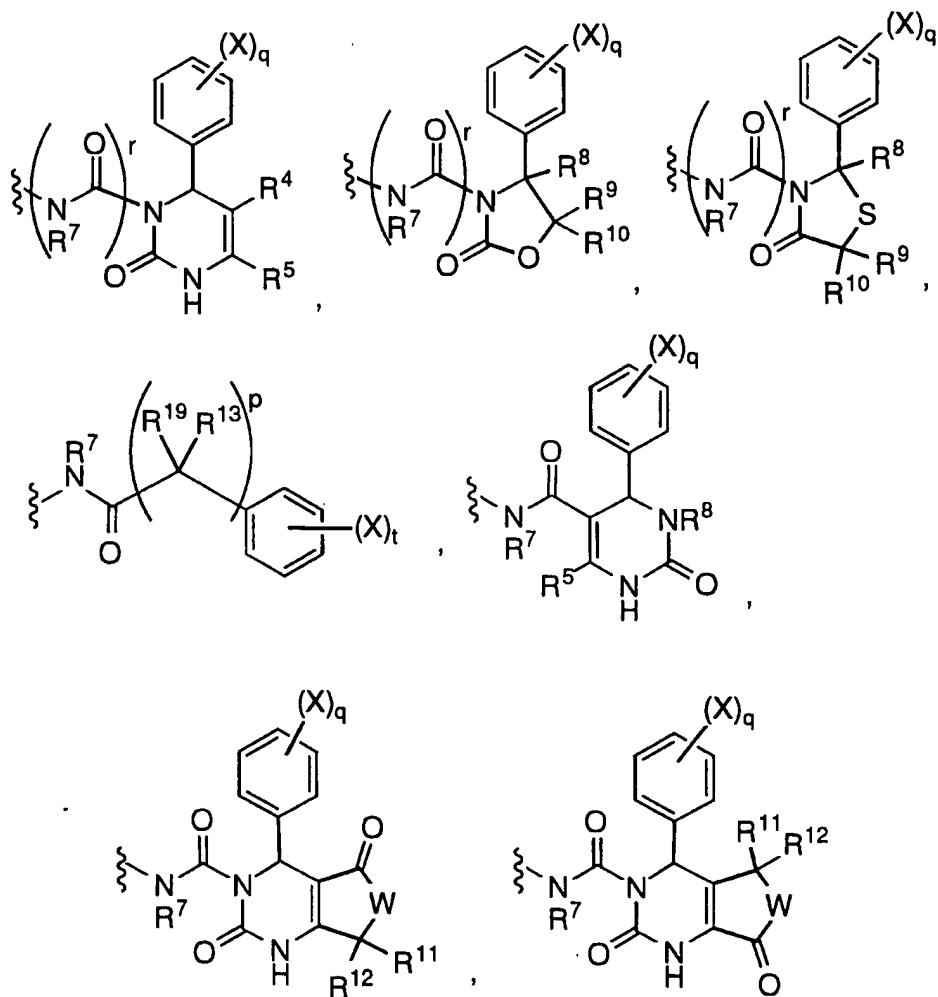
20 equivalents.

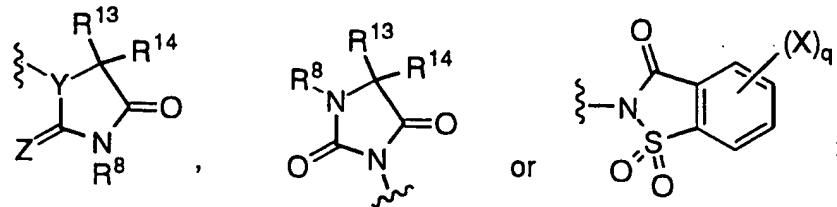
WHAT IS CLAIMED IS:

1. A compound of the formula:



5 wherein Q is selected from





E, G, L and M are each independently selected from hydrogen, C₁-8 alkyl, C₃-8 cycloalkyl, (CH₂)₀-4OR¹⁵, (CH₂)₀-4N(R¹⁶)₂, (CH₂)₀-4CN, (CH₂)₀-4CF₃, (CH₂)₀-4CO₂R¹⁶, (CH₂)₀-4CON(R¹⁶)₂,
 5 (CH₂)₀-4SO₂R¹⁶, or (CH₂)₀-4SO₂N(R¹⁶)₂;

J is selected from hydrogen, C₁-8 alkyl, C₃-8 cycloalkyl, (CH₂)₁-4OR¹⁵, (CH₂)₁-4N(R¹⁶)₂, (CH₂)₁-4CN, (CH₂)₀-4CF₃, (CH₂)₀-4CO₂R¹⁶, (CH₂)₀-4CON(R¹⁶)₂, (CH₂)₀-4SO₂R¹⁶, or
 10 (CH₂)₀-4SO₂N(R¹⁶)₂;

R¹ is selected from unsubstituted, mono- or poly-substituted phenyl wherein the substituents on the phenyl are independently selected from halogen, CF₃, cyano, nitro, N(R¹⁶)₂, NR¹⁶COR¹⁸, NR¹⁶COR²⁰,
 15 NR¹⁶CON(R¹⁸)₂, NR¹⁶CONR¹⁶CON(R¹⁸)₂, NR¹⁶SO₂R¹⁸, NR¹⁶SO₂N(R¹⁸)₂, OR¹⁵, (CH₂)₀-4CO₂R¹⁶,
 (CH₂)₀-4CON(R¹⁶)₂, (CH₂)₀-4SO₂N(R¹⁶)₂, (CH₂)₀-4SO₂R¹⁵,
 (CH₂)₀-4SO₂R²² or
 C₁-4 alkyl; or unsubstituted, mono- or poly-substituted pyridyl,
 20 pyrazinyl, pyrimidinyl, thienyl, thiazolyl, furanyl, isoquinolinyl, quinazolinyl or naphthyl wherein the substituents on the pyridyl, pyrazinyl, pyrimidinyl, thienyl, thiazolyl, furanyl, isoquinolinyl, quinazolinyl or naphthyl are independently selected from CF₃, cyano, nitro, amino, NR¹⁶COR¹⁸, NR¹⁶COR²⁰, NR¹⁶SO₂R¹⁸,
 25 NR¹⁶CONR¹⁶CON(R¹⁸)₂, (CH₂)₀-4CO₂R¹⁶, (CH₂)₀-4CON(R¹⁶)₂, (CH₂)₀-4SO₂N(R¹⁶)₂, (CH₂)₀-4SO₂R¹⁵, (CH₂)₀-4SO₂R²², phenyl, OR¹⁵, halogen, C₁-4 alkyl or C₃-8 cycloalkyl;

R² and R⁷ are each independently selected from hydrogen, C₁-8 alkyl,
 30 C₄-8 cycloalkyl, (CH₂)₀-4CO₂R¹⁶, (CH₂)₀-4CON(R¹⁶)₂,

(CH₂)₀₋₄COR¹⁶, (CH₂)₂₋₄OR¹⁵, (CH₂)₁₋₄CF₃, (CH₂)₀₋₄SO₂R¹⁶,
(CH₂)₀₋₄SO₂N(R¹⁶)₂ or (CH₂)₁₋₄CN;

R³, R⁶, R⁹ and R¹⁰ are each independently selected from hydrogen, C₁₋₈ alkyl, C₃₋₈ cycloalkyl, (CH₂)₂₋₄OR¹⁵ or (CH₂)₀₋₄CF₃;

R⁴ is selected from hydrogen, (CH₂)₀₋₄COR¹⁵, (CH₂)₀₋₄CN, (CH₂)₀₋₄CF₃,
(CH₂)₀₋₄CO₂R¹⁶, (CH₂)₀₋₄CON(R¹⁶)₂, (CH₂)₀₋₄SO₂R¹⁵ or
(CH₂)₀₋₄SO₂N(R¹⁶)₂;

R⁵ is selected from hydrogen, C₁₋₈ alkyl, C₃₋₈ cycloalkyl, (CH₂)₁₋₄OR¹⁵ or (CH₂)₀₋₄CF₃;

R⁸ is selected from hydrogen, C₁₋₈ alkyl, C₃₋₈ cycloalkyl, (CH₂)₂₋₄OR¹⁵ or (CH₂)₀₋₄CF₃;

R¹¹ and R¹² are each independently selected from hydrogen, C₁₋₈ alkyl or C₃₋₈ cycloalkyl;

R¹³ and R¹⁴ are each independently selected from hydrogen, C₁₋₈ alkyl, C₃₋₈ cycloalkyl, (CH₂)₁₋₄OR¹⁵, (CH₂)₀₋₄CF₃, unsubstituted, mono- or poly-substituted phenyl wherein the substituents on the phenyl are independently selected from halogen, CF₃, cyano, nitro, CO₂R¹⁶, OR¹⁵, (CH₂)₀₋₄CON(R¹⁶)₂, (CH₂)₀₋₄CO₂R¹⁶ or C₁₋₄ alkyl; or unsubstituted, mono- or poly-substituted: pyridyl, pyrazinyl, thienyl, furanyl or naphthyl wherein the substituents on the pyridyl, pyrazinyl, thienyl, furanyl or naphthyl are independently selected from CF₃, phenyl, OR¹⁵, halogen, C₁₋₄ alkyl or C₃₋₈ cycloalkyl;

R¹⁵ is selected from hydrogen, C₁₋₈ alkyl, C₃₋₈ cycloalkyl or (CH₂)₀₋₄CF₃;

R¹⁶ and R¹⁸ are each independently selected from hydrogen, C₁₋₈ alkyl, C₄₋₈ cycloalkyl or (CH₂)₁₋₄CF₃;

R¹⁹ is selected from hydrogen, C₁₋₈ alkyl, C₃₋₈ cycloalkyl,
5 (CH₂)₀₋₄OR¹⁵ or (CH₂)₀₋₄CF₃;

R²⁰ is furanyl or C₁₋₈ alkyl furanyl;

R²² is piperazinyl or C₁₋₈ alkylpiperazinyl;

10

W is O or NR¹¹;

each X is independently selected from halogen, cyano, nitro, C₁₋₈ alkyl, C₃₋₈ cycloalkyl, (CH₂)₀₋₄OR¹⁵ or (CH₂)₀₋₄CF₃;

15

Y is CR¹⁵ or N;

Z is hydrogen, oxygen or sulphur;

20

m, n, p and q are each independently an integer from zero to four;
o is an integer from two to five;
r is an integer from zero to one;
t is an integer from zero to five;
or a pharmaceutically acceptable salt thereof.

25

2. The compound of Claim 1, wherein R¹ is selected from unsubstituted, mono- or poly-substituted phenyl wherein the substituents on the phenyl are independently selected from halogen, CF₃, cyano, nitro, N(R¹⁶)₂, NR¹⁶COR¹⁸, NR¹⁶CON(R¹⁸)₂, NR¹⁶SO₂R¹⁸,
30 NR¹⁶SO₂N(R¹⁸)₂, OR¹⁵, (CH₂)₀₋₄CO₂R¹⁶,
(CH₂)₀₋₄CON(R¹⁶)₂, (CH₂)₀₋₄SO₂N(R¹⁶)₂, (CH₂)₀₋₄SO₂R¹⁵ or
C₁₋₄ alkyl; or unsubstituted, mono- or poly-substituted pyridyl, pyrazinyl, thienyl, thiazolyl, furanyl, quinazolinyl or naphthyl wherein the substituents on the pyridyl, pyrazinyl, thienyl, furanyl, quinazolinyl

or naphthyl are independently selected from CF_3 , cyano, nitro, amino, $\text{NR}^{16}\text{COR}^{18}$, $\text{NR}^{16}\text{SO}_2\text{R}^{18}$, $(\text{CH}_2)_{0-4}\text{CO}_2\text{R}^{16}$, $(\text{CH}_2)_{0-4}\text{CON}(\text{R}^{16})_2$, $(\text{CH}_2)_{0-4}\text{SO}_2\text{N}(\text{R}^{16})_2$, $(\text{CH}_2)_{0-4}\text{SO}_2\text{R}^{15}$, phenyl, OR¹⁵, halogen, C₁₋₄ alkyl or C₃₋₈ cycloalkyl; and

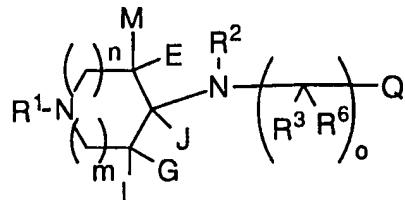
5

R^4 is selected from $(\text{CH}_2)_{0-4}\text{COR}^{15}$, $(\text{CH}_2)_{0-4}\text{CN}$, $(\text{CH}_2)_{0-4}\text{CF}_3$, $(\text{CH}_2)_{0-4}\text{CO}_2\text{R}^{16}$, $(\text{CH}_2)_{0-4}\text{CON}(\text{R}^{16})_2$, $(\text{CH}_2)_{0-4}\text{SO}_2\text{R}^{15}$ or $(\text{CH}_2)_{0-4}\text{SO}_2\text{N}(\text{R}^{16})_2$;

or a pharmaceutically acceptable salt thereof.

10

3. The compound of Claim 1, of the formula



wherein

15 E, G, L, M and J are each independently selected from hydrogen, C₁₋₈ alkyl, C₃₋₈ cycloalkyl, or $(\text{CH}_2)_{0-4}\text{CF}_3$;

20 R¹ is selected from unsubstituted, mono-, di- or tri-substituted phenyl wherein the substituents on the phenyl are independently selected from halogen, CF_3 , cyano, nitro, $\text{N}(\text{R}^{16})_2$, $\text{NR}^{16}\text{COR}^{18}$, $\text{NR}^{16}\text{COR}^{20}$, $\text{NR}^{16}\text{CON}(\text{R}^{18})_2$, $\text{NR}^{16}\text{CONR}^{16}\text{CON}(\text{R}^{18})_2$, $\text{NR}^{16}\text{SO}_2\text{R}^{18}$, $\text{NR}^{16}\text{SO}_2\text{N}(\text{R}^{18})_2$, OR¹⁵, $(\text{CH}_2)_{0-4}\text{CO}_2\text{R}^{16}$, $(\text{CH}_2)_{0-4}\text{CON}(\text{R}^{16})_2$, $(\text{CH}_2)_{0-4}\text{SO}_2\text{N}(\text{R}^{16})_2$, $(\text{CH}_2)_{0-4}\text{SO}_2\text{R}^{15}$, $(\text{CH}_2)_{0-4}\text{SO}_2\text{R}^{22}$ or

25 C₁₋₄ alkyl; or unsubstituted, mono-, di- or tri-substituted pyridyl, pyrazinyl, pyrimidinyl, thienyl, thiazolyl, furanyl, isoquinolinyl, quinazolinyl or naphthyl wherein the substituents on the pyridyl, pyrazinyl, pyrimidinyl, thienyl, thiazolyl, furanyl, isoquinolinyl, quinazolinyl or naphthyl are independently selected from CF_3 , cyano,

nitro, amino, $NR^{16}COR^{18}$, $NR^{16}COR^{20}$, $NR^{16}SO_2R^{18}$,
 $NR^{16}CONR^{16}CON(R^{18})_2$, $(CH_2)_{0-4}CO_2R^{16}$, $(CH_2)_{0-4}CON(R^{16})_2$,
 $(CH_2)_{0-4}SO_2N(R^{16})_2$, $(CH_2)_{0-4}SO_2R^{15}$, $(CH_2)_{0-4}SO_2R^{22}$, phenyl, OR^{15} ,
halogen,
5 C₁₋₄ alkyl or C₃₋₈ cycloalkyl;

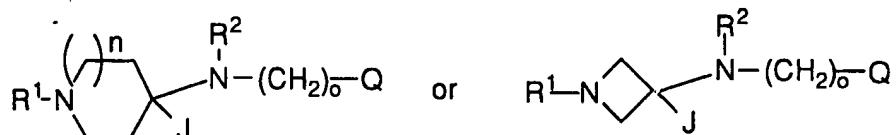
R² and R⁷ are each independently selected from hydrogen, C₁₋₈ alkyl, C₄₋₈ cycloalkyl or (CH₂)₁₋₄CF₃;

10 R¹³ and R¹⁴ are each independently selected from hydrogen, C₁₋₈ alkyl, C₃₋₈ cycloalkyl, (CH₂)₁₋₄OR¹⁵, (CH₂)₀₋₄CF₃, unsubstituted, mono-, di- or tri-substituted phenyl wherein the substituents on the phenyl are independently selected from halogen, CF₃, cyano, nitro, amino, OR¹⁵, (CH₂)₀₋₄CON(R¹⁶)₂,
15 (CH₂)₀₋₄CO₂R¹⁶ or C₁₋₄ alkyl; or unsubstituted, mono-, di- or tri-substituted: pyridyl, thienyl, furanyl or naphthyl wherein the substituents on the pyridyl, thienyl, furanyl or naphthyl are independently selected from CF₃, phenyl, OR¹⁵, halogen, C₁₋₄ alkyl or C₃₋₈ cycloalkyl;

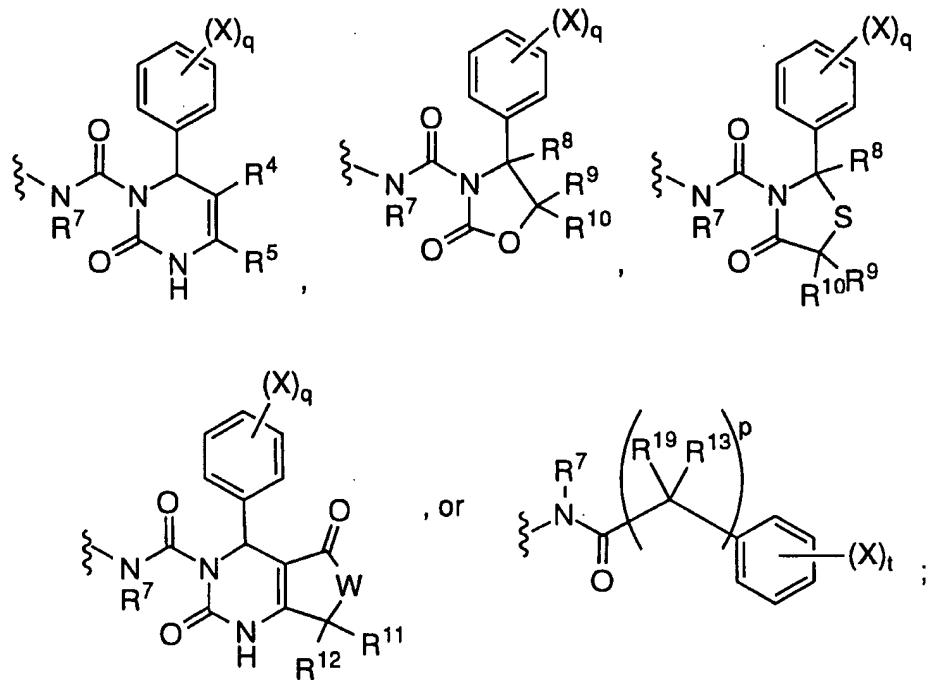
20 n is an integer from zero to two;
m is an integer from zero to one; and
o is an integer from two to four;
or a pharmaceutically acceptable salt thereof.

25

4. The compound of Claim 3, of the formula selected from



wherein Q is selected from



R¹ is selected from unsubstituted, mono-, di- or tri-substituted phenyl wherein the substituents on the phenyl are independently selected from halogen, CF₃, cyano, nitro, N(R¹⁶)₂, NR¹⁶COR¹⁸, NR¹⁶COR²⁰,

5 NR¹⁶CON(R¹⁸)₂, NR¹⁶SO₂R¹⁸, OR¹⁵, (CH₂)₀₋₂CO₂R¹⁶, (CH₂)₀₋₂CON(R¹⁶)₂, (CH₂)₀₋₂SO₂R¹⁵, (CH₂)₀₋₂SO₂N(R¹⁶)₂, (CH₂)₀₋₂SO₂R²² or C₁₋₄ alkyl; or unsubstituted, mono- or di-substituted pyridyl or pyrimidinyl wherein the substituents on the pyridyl or the pyrimidinyl are independently selected from CF₃, cyano, nitro, amino, NR¹⁶COR¹⁸,

10 NR¹⁶COR²⁰, NR¹⁶CON(R¹⁸)₂, NR¹⁶SO₂R¹⁸, (CH₂)₀₋₂CO₂R¹⁶, (CH₂)₀₋₂CON(R¹⁶)₂, (CH₂)₀₋₂SO₂R¹⁵, (CH₂)₀₋₂SO₂N(R¹⁶)₂, OR¹⁵, halogen, (CH₂)₀₋₂SO₂R²² or C₁₋₄ alkyl; or unsubstituted thiazolyl; or unsubstituted isoquinolinyl;

15 R² and R⁷ are each independently selected from hydrogen, C₁₋₆ alkyl, C₄₋₆ cycloalkyl or (CH₂)₁₋₄CF₃.

R^4 is selected from hydrogen, COR^{15} , $(CH_2)_{0-2}CO_2R^{16}$, SO_2R^{15} or

$(CH_2)_{0-2}CON(R^{16})_2;$

R^5 is selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, $(CH_2)_{1-3}OR^{15}$ or $(CH_2)_{0-3}CF_3$; and

5

R^8 , R^9 and R^{10} are each independently selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, $(CH_2)_{2-4}OR^{15}$ or $(CH_2)_{0-2}CF_3$;

10 R^{13} is selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, $(CH_2)_{2-4}OR^{15}$, $(CH_2)_{0-2}CF_3$ or unsubstituted, mono- or di-substituted phenyl wherein the substituents on the phenyl are independently selected from halogen, CF₃, cyano, nitro, amino, OR¹⁵, CO₂R¹⁶ or C₁₋₄ alkyl;

15 R^{15} is selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl or $(CH_2)_{0-2}CF_3$;

R^{16} and R^{18} are each independently selected from hydrogen, C₁₋₆ alkyl, C₄₋₆ cycloalkyl or $(CH_2)_{1-2}CF_3$;

20

R^{19} is selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, $(CH_2)_{0-4}OR^{15}$ or $(CH_2)_{0-2}CF_3$;

p is an integer from one to two;

25 q is an integer from zero to three;

t is an integer from zero to four;

or a pharmaceutically acceptable salt thereof.

5. The compound of Claim 4, selected from

30

4S-4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid (2-(2-(4-trifluoromethylpyrimidyl)piperidin-4-ylamino)ethyl)amide;

4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(4-trifluoromethylpyrimidinyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

5 4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-pyrimidinylpiperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

10 4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-pyrimidinylpiperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

15 4S-4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid (2-(2-pyrimidinylpiperidin-4-ylamino)ethyl)amide;

20 4S-4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid (2-(2-thiazolylpiperidin-4-ylamino)ethyl)amide;

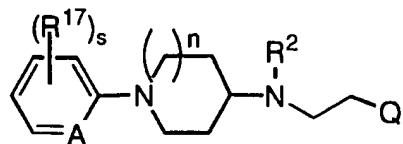
25 4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-cyanophenyl)azetidin-3-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

30 4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(1-isoquinolinyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

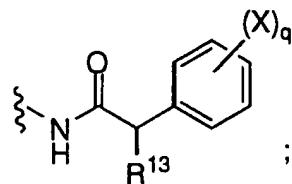
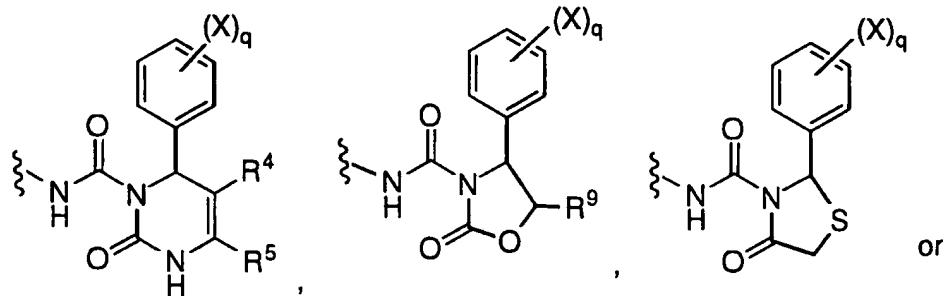
4S-4-(3,4-Difluorophenyl)-2-oxo-3-(2-(2-carboxymethylphenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydro-4H-furo[3,4d]pyrimidine;

5 and the pharmaceutically acceptable salts thereof.

6. The compound of Claim 4, of the formula



10 wherein Q is selected from



A is C-R¹⁷ or N;

15 R² is selected from hydrogen or CH₂CF₃;

R⁹ is selected from hydrogen or C₁₋₄ alkyl;

each R¹⁷ is independently selected from hydrogen, halogen, CF₃, cyano, nitro, amino, NR¹⁶COR¹⁸, NR¹⁶CON(R¹⁸)₂, NR¹⁶CONR¹⁶CON(R¹⁸)₂, NR¹⁶SO₂R¹⁸, NR¹⁶COR²⁰, OR¹⁵, CO₂R¹⁶, CON(R¹⁶)₂, SO₂N(R¹⁶)₂, SO₂R¹⁵ or C₁₋₄ alkyl;

5

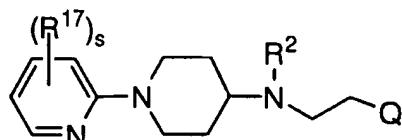
each X is halogen;

n is an integer from zero to one; and

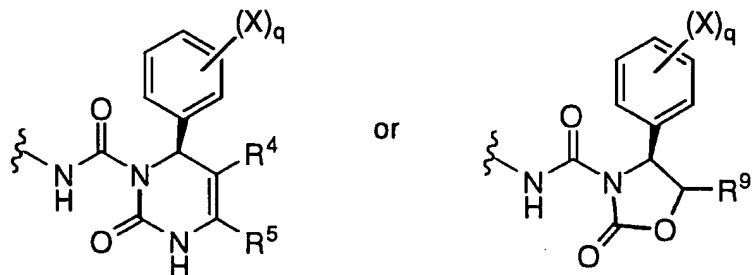
q and s are each independently an integer from zero to two;

10 or a pharmaceutically acceptable salt thereof.

7. The compound of Claim 6, of the formula



15 wherein Q is selected from



or a pharmaceutically acceptable salt thereof.

8. The compound of claim 7, selected from

20

4S-4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid
(2-(2-(3-trifluoromethylpyridyl)piperidin-4-ylamino)ethyl)amide;

4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(3-trifluoromethylpyridyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

5 4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-(3-methylpyridyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

10 4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-(5-methylpyridyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

15 4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(5-trifluoromethylpyridyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

20 4S-4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid (2-(2-(5-trifluoromethylpyridyl)piperidin-4-ylamino)ethyl)amide;

25 4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(4-trifluoromethylpyridyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

30 4S-4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid (2-(2-(4-trifluoromethylpyridyl)piperidin-4-ylamino)ethyl)amide;

4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(6-methylpyridinyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(6-bromopyridyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

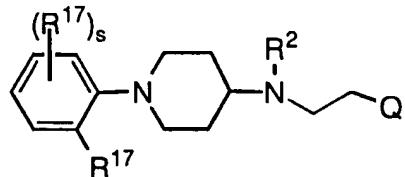
4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-(3,6-bistrifluoromethylpyridyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

5 4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-(6-N-acetylaminopyridyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

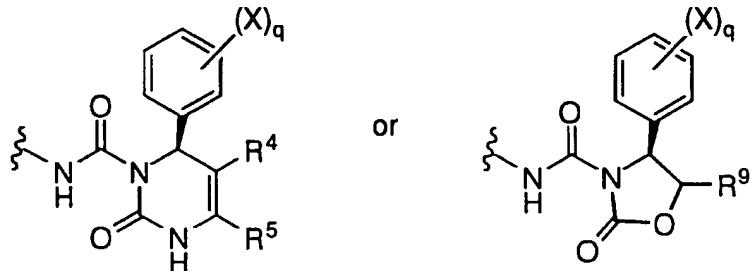
and the pharmaceutically acceptable salts thereof.

10

9. The compound of Claim 6, of the formula



wherein Q is selected from



15 each R17 is independently selected from hydrogen, halogen, CF3, cyano, nitro, amino, NHCONH2, NHCONHCONH2, NHCO-furanyl, NHCONH C1-4 alkyl, C1-4 alkoxy, OCF3, OCH2CF3, CO2-C1-4 alkyl, CONH2, SO2NH2, SO2C1-4 alkyl, NHSO2C1-4 alkyl, SO2C1-4 alkylpiperazinyl or C1-4 alkyl;

20

or a pharmaceutically acceptable salt thereof.

10. The compound of Claim 9, selected from
N-(2-(1-(2-cyanophenyl)piperidin-4-ylamino)ethyl)-2-(3,4-
difluorophenyl)acetamide;

5 4-(3,4-difluorophenyl)-6-methoxymethyl-3-(2-(1-(2-nitrophenyl)-piperidin-
4-ylamino)ethylcarbamoyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-
carboxylic acid methyl ester;

10 3-(2-(1-(2-cyanophenyl)piperidin-4-ylamino)ethylcarbamoyl)-4-(3,4-
difluorophenyl)-6-methoxymethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-
carboxylic acid methyl ester;

15 4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(1-o-tolylpiperidin-4-
ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid
methyl ester;

20 4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid (2-(1-(2-
cyanophenyl)piperidin-4-ylamino)ethyl)amide;

25 3-(2-(1-(2-cyano-4-trifluoromethylphenyl)piperidin-4-
ylamino)ethylcarbamoyl)-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-
1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

30 3-(2-(1-(2-cyano-4-methylphenyl)piperidin-4-ylamino)ethylcarbamoyl)-4-(3,4-
difluorophenyl)-6-methoxymethyl-2-oxo-1,2,3,4-
tetrahydropyrimidine-5-carboxylic acid methyl ester;

35 3-(2-(1-(4-cyanophenyl)piperidin-4-ylamino)ethylcarbamoyl)-4-(3,4-
difluorophenyl)-6-methoxymethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-
carboxylic acid methyl ester;

3-(2-(1-(2-cyano-4-fluorophenyl)-piperidin-4-ylamino)ethylcarbamoyl)-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

5 4-(3,4-difluorophenyl)-3-(2-(1-(2-methoxycarbonylphenyl)piperidin-4-ylamino)ethylcarbamoyl)-6-methoxymethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

10 4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid (2-((1-(2-cyanophenyl) piperidin-4-yl)-(2,2,2-trifluoroethyl)amino)ethyl)amide;

15 4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(1-(2,2,2-trifluoroethoxy)phenyl) piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

20 4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid (2-(1-(2-cyanophenyl) pyrrolidin-3-ylamino)ethyl)amide;

25 2-(3,4-difluorophenyl)-N-(2-(1-(2-nitrophenyl)piperidin-4-ylamino)ethyl)acetamide;

30 2-(3,4-difluorophenyl)-4-oxothiazolidine-3-carboxylic acid (2-(1-(2-cyanophenyl) piperidin-4-ylamino)ethyl)amide;

4-(3,4-difluorophenyl)-5-methyl-2-oxo-oxazolidine-3-carboxylic acid (2-(1-(2-cyanophenyl) piperidin-4-ylamino)ethyl)amide;

3-(2-(1-(2-carbamoylphenyl)piperidin-4-ylamino)ethylcarbamoyl)-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

5 4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid (2-(1-(2-carbamoylphenyl) piperidin-4-ylamino)ethyl)amide;

10 4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid (2-(1-(4-fluoro-2-methoxycarbonylphenyl)piperidin-4-ylamino)ethyl)amide; or

15 4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid (2-(1-(2-methoxycarbonylphenyl)piperidin-4-ylamino)ethyl)amide;

and the pharmaceutically acceptable salts thereof.

15 11. The compound of Claim 9, selected from

20 4S-4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid (2-(1-(2-methoxyphenyl)piperidin-4-ylamino)ethyl)amide;

25 4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(1-(2-trifluoromethylphenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

30 4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(1-(4-methoxyphenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

4S-4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid (2-(1-(4-methoxyphenyl)piperidin-4-ylamino)ethyl)amide;

4S-4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid (2-(2-(2,4-difluorophenyl)piperidin-4-ylamino)ethyl)amide;

4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(1-(2,4-difluorophenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

5 4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(1-(2-sulfonamidophenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

10 4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(1-(2-methanesulfonylphenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

15 4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(1-(2-trifluormethylphenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

20 4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(1-(2-cyanophenyl)pyrrolodin-3-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

25 4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(1-(3-fluorophenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

30 4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(1-(4-carboxymethylphenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

35 4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(1-(2-cyano-5-fluorophenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(1-(3,5-difluorophenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

5 4S-4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid (2-(1-(3,5-difluorophenyl)piperidin-4-ylamino)ethyl)amide;

10 4S-4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid (2-(1-(2-carboxymethylphenyl)piperidin-4-ylamino)ethyl)amide;

15 4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-(3,6-bistrifluoromethylpyridyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

20 4S-4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid (2-(1-(2-cyano-4-fluorophenyl)piperidin-4-ylamino)ethyl)amide;

25 4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-(3,5-dichlorophenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

30 4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-(2-N-sulfonylmethylaminophenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-(2-aminophenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-(2-nitrophenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-(2-N-carboxamidoaminophenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

5 4S-4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-(2-N-1-imidocarbonic diamidyl) phenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester

4S-4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid (2-(1-(2-nitrophenyl)piperidin-4-ylamino)ethyl)amide;

10 4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-(2-N-(2-furanyl)carbonylaminophenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

15 4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-(4-N-methylpiperazinyl)sulfonylphenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

20 4S-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-(2-carboxymethylphenyl)piperidin-4-yl-1-methylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

25 (4S)-4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-(2-(2-(1-N-(3-N-methylureyl)phenyl)piperidin-4-ylamino)ethylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester;

and the pharmaceutically acceptable salts thereof.

30 12. A pharmaceutical composition comprising the compound of Claim 1 and a pharmaceutically acceptable carrier.

13. The composition of Claim 12 further comprising a testosterone 5-alpha reductase inhibitor.

35

14. The composition of Claim 13, wherein the testosterone 5-alpha reductase inhibitor is a type 1, a type 2, both a type 1 and a type 2 or a dual type 1 and type 2 testosterone 5-alpha reductase inhibitor.

5 15. The composition of Claim 14, wherein the testosterone 5-alpha reductase inhibitor is a type 2 testosterone 5-alpha reductase inhibitor.

10 16. The composition of Claim 15, wherein the testosterone 5-alpha reductase inhibitor is finasteride.

17. A pharmaceutical composition made by combining a compound of Claim 1 and a pharmaceutically acceptable carrier.

15 18. A process for making a pharmaceutical composition comprising combining a compound of Claim 1 and a pharmaceutically acceptable carrier.

20 19. A method of treating benign prostatic hyperplasia in a subject in need thereof which comprises administering to the subject a therapeutically effective amount of the compound of Claim 1.

25 20. The method of Claim 19, wherein the compound additionally does not cause a fall in blood pressure at dosages effective to alleviate benign prostatic hyperplasia.

21. The method of Claim 19, wherein the compound is administered in combination with a testosterone 5-alpha reductase inhibitor.

30 22. The method of Claim 21, wherein the testosterone 5-alpha reductase inhibitor is finasteride.

23. A method of treating benign prostatic hyperplasia in a subject in need thereof which comprises administering a therapeutically effective amount of the composition of Claim 12.

5 24. The method of Claim 23, wherein the composition further comprises a therapeutically effective amount of a testosterone 5-alpha reductase inhibitor.

10 25. A method of relaxing lower urinary tract tissue in a subject in need thereof which comprises administering to the subject a therapeutically effective amount of the compound of Claim 1.

15 26. The method of Claim 21, wherein the compound additionally does not cause a fall in blood pressure at dosages effective to relax lower urinary tract tissue.

20 27. The method of Claim 27, wherein the compound is administered in combination with a testosterone 5-alpha reductase inhibitor.

28. The method of Claim 23, wherein the testosterone 5-alpha reductase inhibitor is finasteride.

29. A method of treating a condition which is susceptible to treatment by antagonism of the alpha 1a receptor which comprises administering to a subject in need thereof an amount of the compound of Claim 1 effective to treat the condition.

30 30. A method of eliciting an alpha 1a antagonizing effect in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of the compound of Claim 1.

INTERNATIONAL SEARCH REPORT

International application No. PCT/US98/12567

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/258, 269, 318, 321, 326; 544/278, 280, 316, 317; 546/194, 209

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,574,044 A (THOMPSON et al.) 12 November 1996, entire columns 3-10.	1-30
A	US 5,618,827 A (OXFORD) 08 April 1997, entire columns 1-5.	1-30

<input type="checkbox"/>	Further documents are listed in the continuation of Box C.	<input type="checkbox"/>	See patent family annex.
* A*	Special categories of cited documents:	* T*	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
* A*	document defining the general state of the art which is not considered to be of particular relevance	* X*	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
* B*	earlier document published on or after the international filing date	* Y*	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
* L*	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	* Z*	document member of the same patent family
* O*	document referring to an oral disclosure, use, exhibition or other means		
* P*	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
11 SEPTEMBER 1998	OCT 13 1998

Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer  YOGENDRA N. GUPTA Telephone No. (703) 308-1235
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/12567

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

A61K 31/445, 31/505; C07D 211/18, 239/34, 491/08, 487/04, 401/12, 411/12, 413/12

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

514/258, 269, 318, 321, 326; 544/278, 280, 316, 317; 546/194, 209